EU Navigate

Supporting older people with cancer

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Part of WP 3: Pragmatic Randomized Controlled Trial Effectiveness study

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This deliverable includes the following documents related to the protocol of the International Pragmatic Randomised Controlled trial of the NavCare-EU intervention for older people with cancer and their family caregivers:

- the Study Protocol;
- the preliminary Statistical Analysis Plan;
- the ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt.

Study protocol for an International Pragmatic Randomised Controlled trial of the NavCare-EU intervention for older people with cancer and their family caregivers

Acronym: NavCare-EU trial

Funding: This project received funding from the European Union (grant no. 101057361).

First entry: December 21, 2021
Last entry: August 04, 2023
Protocol structure based on SPIRIT guidelines for protocol of clinical trials, and further informed by Consort reporting guidelines for pragmatic trials.

EU NAVIGATE consortium

1. VRIJE UNIVERSITEIT BRUSSEL (Belgium)
2. THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD, OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN (IE)
3. UNIWERSYTET JAGIELLONSKI (Poland)
4. STICHTING VUMC (NL)
5. UNIVERSIDADE DE COIMBRA (Portugal)
6. UNIVERSITEIT GENT (BE)
7. UNIVERSITY OF BRITISH COLUMBIA - OKANAGAN (CA)
8. EUROPEAN CANCER ORGANISATION (BE)
9. EUROPEAN ASSOCIATION OF PALLIATIVE CARE (BE)
10. AGE PLATFORM EUROPE (BE)
11. LEGA ITALIANA PER LA LOTTA CONTRO I TUMORI DI MILANO (IT)

HISTORY OF MODIFICATIONS

Every modification to this study protocol must be reported in the table below, to ensure the traceability and transparency of the study's progress and findings.

Date	Author	Note
Sept 21th, 2021	Lieve Van den Block, Lara Pivodic, Rose Miranda, Tinne Smets	First version of protocol in EU NAVIGATE proposal submitted to EU
Sept 19-20, 2023	All partners	Consortium meeting Bruges: discussion of the trial methodology
Nov 11th 2022	Lara Pivodic	First draft of protocol for ethics approval sent to VUB/UGent team for review
Nov 29th 2022	All research partners	The first draft of protocol sent to all research partners and discussed in the WP Research meeting of Nov 29, 2022
Dec 6, 2022	Tinne Smets / Lieve Van den Block	Feedback from WP Research meeting of 28/11/2022 integrated in protocol
Dec 2022	Joni Gilissen	Delivered section "Pilot-testing of the NavCare-EU intervention"
Dec 23, 2022	Tinne Smets / Lieve Van den Block	New version of protocol sent to all research partners for written feedback
Jan, 2023	Team Ireland, team Italy, team Canada	Written feedback on protocol
Jan 16th, 2023	All research partners	New version of protocol discussed in the WP Research meeting of Jan 16th, 2023
Febr, 2023	Team Portugal	Written feedback on protocol
Febr-March 2023	Tinne Smets / Lieve Van den Block	Feedback from partners integrated in protocol
Febr-March 2023	Fien Van Campe/Chelsea Vinckier/Lara Pivodic/Lieve Van den Block	Adaptations to section Outcomes
March 2023	Fien Van Campe/Chelsea Vinckier	Adaptations to section "Pilot-testing of the NavCare-EU intervention"
March 2023	Chelsea Vinckier / Tinne Smets	Delivered Data Management Plan (Appendix 9)
March 2023	Team Netherlands	Process evaluation integrated in protocol + written feedback on protocol Delivered Process evaluation plan (Appendix 10)
March 2023	Team Portugal	Delivered Subgroup analysis plan (Appendix 11)
March 2023	Peter May	Delivered Health Economic analysis plan (Appendix 9)
March 2023	Rose Miranda, with	Delivered Statistical Analysis plan +

	input from Trial Statistician, Lieve Van den Block, Lara Pivodic, Tinne Smets	(Appendix 10)
March 2023	Fien Van Campe, Helena Du Cheyne	Lay-out and reference list
April-June	All researchers	Final adaptations and corrections before submissions to Ethical Committees
July-August	Chelsea Vinckier, Lieve Van den Block, Tinne Smets, reviewed by all researchers	Adaptations pilot study and adaptations after remarks from Ethics: [EC remarks and associated adaptations to the protocol that have international implications were communicated to and approved by the consortium during an online research meeting on12/0872023]
17/08/2023	Chelsea Vinckier	'Public Interest' principal for data of non-eligible participants
21/08/2023	Fien Van Campe	Adaptations on the discontinuation of the intervention paragraph on the basis of feedback on deliverable 1.2 Quality Assurance Manual including ethics and data management plan

WHO Trial registration data set.

1. **Primary Registry and Trial Identifying Number**

The study will be registered at www.clinicaltrial.gov, a registry and results database of clinical studies of human participants maintained by the American National Library of Medicine and National Institutes of Health. (add trial identifying number after registration)

2. **Data of Registration in Primary Registry**

To be decided

3. **Secondary Identifying Numbers**

Grant agreement No: 101057361.

4. **Source(s) of Monetary or Material Support**

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No. 101057361.
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5. **Contact for public queries**

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6. **Contact for scientific queries**

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7. **Public title**

International study to evaluate a navigation program for older persons with cancer and their family caregivers (EU NAVIGATE study).

8. **Scientific title**

Study protocol for an International Pragmatic Randomised Controlled trial of the NavCare-EU intervention for older people with cancer and their family caregivers

Role and responsibilities

All authors contributed to the refinement of the study protocol and approved the final version.

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[7] Lega Italiana per la lotta contro i tumori di Milano, Milano, Italy
[8] End-of-life Care Research Group, Vrije Universiteit Brussel (VUB) & Ghent University, Brussels, Belgium; Department of Public Health and Primary Care, Ghent University, Brussels, Belgium.

The funder of the trial has no role in the collection, management, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the report for publication.

Organisational structure and responsibilities

Principal investigators

The principal investigator (PI) Prof. Lieve Van den Block (VUB) is leading the project at the management level and serves as the gateway between the Supervisory and the Management board and the partners. She is supported by the Prof. Tinne Smets (VUB), Prof. Lara Pivodic (VUB), Dr. Joni Gilissen (VUB & UGent) and Dr Rose Miranda (VUB),

and PhD students.
The other PIs of the partners are Prof. Bregje Onwuteaka-Philipsen BD, Prof. Katarzyna Szczerbińska, Prof. Andrew Davies, Prof. Kenneth Chambaere, Prof. Barbara Gomes, Prof. Barbara Pesut, and Davide Ferraris
Together they are responsible for the

- Design and conduct of EU NAVIGATE trial
- Preparation of RCT protocol and revisions
- Organising supervisory board meetings, management board meetings and consortium meetings
- Study planning
- Publication of study reports

Research assistant/PhD student

- Screening and recruitment of eligible older people with cancer and family caregivers for the study
- data collection within a country, assistance for participants when completing questionnaires
- data input

Overall (international) trial manager

- assuring trial quality and regular monitoring in accordance with GCP principles.
- ask all national partners participating to the trial study (the national trial managers) to provide regular updates in trial progress, recruitment rate, implementation, and data collection according to a predefined structure and template, and report in each Management Board meeting.

National trial managers

- assistance with ethical committee applications in each site
- responsible for trial master file in each site
- monitoring trial progress, recruitment rate, implementation, and data collection
- study planning
- follow up of adherence to the study protocol

Ethics Evaluator (external to the project)

- monitor the ethical aspects of the RCT study, including data management and privacy concerns
- provide evaluation and advice on ethical, legal, data protection and data management issues based on an audit of the reporting by the different national trial managers to the Overall Trial Manager and the independent trial monitors in the different countries
- Ethical evaluation will be done shortly after the start of the trial study, and at least at three
  follow-up occasions.

Trial monitor

- The trial monitoring visits will be conducted by national independent trial monitors.

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1. Introduction

1.1. Background and rationale

The impact of cancer on older adults and their families

As is well known, cancer mostly affects older adults. EU estimates from 2020 reveal that 62% of new diagnoses and 76% of deaths occur in people over 65 years old.[1] Improvements in cancer treatments over the last decades that prolong survivorship, combined with steady population ageing, mean that a growing number of older cancer patients will live longer and manage cancer and its effects as a chronic health condition until the end of life.[2] When speaking of older cancer patients, this proposal considers those aged 70 years or over, following references of the European Organisation for Research and Treatment of Cancer.[3] Although older people with cancer are a diverse population,[4] evidence suggests that cancer and cancer treatment impact them differently than younger counterparts, leading to health-related suffering, and poor quality of life and well-being throughout their trajectory. For older cancer patients, the boundaries between survivorship, supportive, palliative and end-of-life care are not clear-cut, and it is important to ensure the necessary services and resources can be provided throughout the care continuum. This project follows the definitions of MASCC[5] and WHO[6] in defining supportive and palliative care: Supportive care in cancer is the prevention and management of the adverse effects of cancer and its treatment, including management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. It aims to improve the quality of rehabilitation, secondary cancer prevention, survivorship, and end-of-life care. Palliative care is an approach that improves the quality of life of patients and families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through early identification, correct assessment and treatment of pain and other problems, physical, psychosocial, or spiritual. Survivorship is considered to span the time between diagnosis and the end of life. The term “survivor” or “survivorship” is used to describe a population of people with a cancer diagnosis.[5]

Next to the direct health impact of cancer, many older patients are affected by serious late and long-term side effects of cancer treatments, many of which worsen geriatric problems such as bone loss, insomnia or cognitive problems[7]. Many older cancer patients are affected by conditions for which age is the single largest risk factor, such as multimorbidity and frailty[8] influencing survival, quality of life, and health care costs.[9,10] Next to medical and physical concerns, unmet needs in the emotional, social and practical domains also negatively impact quality of life and well-being. Older age is associated with increased risk of poverty, social isolation and minimal social support.[11,12] Moreover, older adults and their families are often unaware of the health and social services available to them in the community which contributes to inequitable access to care and health inequalities.[13,14] Family caregivers of older cancer patients also experience considerable strain and burden that limit their health, quality of life and well-being.[15] Research indicates that they are at risk of severe physical and psychological distress that needs to be addressed alongside the patient’s needs.[16]

Even though older people and their family caregivers are disproportionately affected by cancer incidence and mortality compared to younger middle-aged patients, they are highly under-represented in cancer clinical trials.[17] Consequently, many insights gained from current cancer research are not transferable to older cancer populations, and existing interventions are insufficiently validated or adapted to the specific needs of this population.

Interventions to address the needs of older cancer patients and their family caregivers across the continuum of supportive, palliative, survivorship, and end-of-life care, need to consider and work with challenging characteristics of current cancer care provision in Europe. First, cancer care is highly fragmented and complex and difficult to navigate for patients and family carers, which compromises care coordination and continuity. Patients and families report significant problems in obtaining information and identifying and accessing social support services, including financial and practical help.[13] Second, access to high-quality survivorship, supportive, palliative, and end-of-life care is more limited for older cancer patients compared to younger patients,[18] as well as for those living in rural or materially deprived areas,[19] and people with lower educational and/or socioeconomic status.[20] Third, while cancer care in Europe is highly advanced in achieving cure or prolonging people's lives, it has a limited focus on the psychological, social, existential, and practical needs of patients and families. Current cancer care services also insufficiently address the needs of family carers, who fulfil essential care tasks, provide practical and emotional help, and help patients in navigating health and social care.

Need for innovative care concepts and approaches across the continuum of survivorship, palliative, supportive, and end-of-life care: the potential of patient and family navigation

To sustainably meet the increasing demand for high-quality survivorship, supportive, palliative, and end-of-life care within existing EU healthcare systems, contemporary cancer care for older populations needs an innovative, effective, and cost-effective concept or approach. It cannot be department-centric (e.g., tied to hospital, home care or a medical specialty), but must operate across and actively reach out to the variety of environments in which diverse groups of older cancer patients and their family caregivers receive health and social care, ensuring early and equitable access.[17] Furthermore, the heterogeneity of older cancer patients' needs requires a highly adaptable intervention, including the possibility of telehealth alongside face-to-face contacts to reach people in rural areas or those who need to isolate (e.g., in a pandemic). Navigation interventions or programs hold promise to meet these needs. Navigation interventions can be regarded as non-pharmacological interventions that aim to support, educate, and empower patients (and in some programs also families), and \address individual and community barriers to cancer-related diagnostics, treatment, and care to ensure timely access to needed services and resources. Their central component is a patient navigator, a dedicated person with or without a health-related background (e.g., volunteers, nurses, social workers, community health workers) who engages with patients on an individual basis. Navigators are sometimes also called patient advisors, coaches, or linked workers.[21] Although there may be some overlap, navigation can be distinguished from care management and care coordination as navigation is a much broader, more supportive role, grounded in frameworks of patient empowerment and health promotion.[22] Patient navigators also differ from care managers in that they are typically not an integral member of a care team but instead help with navigating across services and advocate for missing services with a focus on removing barriers to care. Navigation was originally developed in the early 90ies in Harlem, New York to address individual and community barriers and health disparities related to cancer care, particularly regarding screening and early diagnosis.[23,24] Since then, patient navigation programs with varying features have been developed and tested,[21,25] most in the US and Canada. In Europe, hardly any cancer navigation services have been developed, let alone tested using high-quality research methods.

Existing evidence for patient and family navigation

Scientific evidence mainly comes from the US and Canada and suggests favourable feasibility and effectiveness, and promising results of cost-effectiveness for patient

navigation in cancer care, specifically during the beginning phases of illness, i.e. cancer screening and diagnosis, and more recently in improving cancer treatment and care.[23,24] Evidence for its use in supportive, palliative, end-of-life or survivorship care is much weaker (72% of studies of navigation program in cancer focused on the early phases)[23] and particularly in older cancer populations.[13] We identified only two existing navigation programs that focused on navigation in the post-diagnostic phases of treatment and care for older people. One concerned a lay navigation program focused on patients in geriatric oncology departments in the US, i.e. Patient Care Connect Program.[22] The second, Nav-Care developed by Pesut & Duggleby, was highly innovative in focusing on the patient together with the family caregivers and in operating across settings and diseases stages.[14,26,27] The research consortium of EU NAVIGATE reviewed this existing evidence, evaluated the potential 'fit' of existing interventions for Europe and particularly Europe's different health care systems, and the relevance to the main strategic health objectives of the EC and the Health call of the Work Programme 2021-2022 Horizon Europe. Based on this, we decided to adapt the Canadian Nav-Care intervention to the EU context, implement it under 'real world' circumstances in different countries with different health care contexts, and evaluate it using a high-quality research design. As the health care, economic, and geographical contexts in Europe differ from those in Canada, building such high-quality scientific evidence is essential for establishing clear recommendations for the implementation of patient and family navigation in different EU countries with a view to generating the most favourable outcomes for older cancer patients and their family. As the very nature of patient navigation (implying low-threshold access and creation of links between patients, families and health and social services) requires their firm integration in existing healthcare contexts, any evaluation of the effectiveness of a navigation intervention must be embedded in 'real-world' healthcare contexts.[28]

Existing evidence concerning the feasibility and effects of Nav-Care©

Nav-Care© developed by Pesut & Duggleby (henceforth called Nav-Care) is a person- and family-centered navigation intervention, developed over the past 13 years for older adults with a variety of chronic illnesses of which cancer was the most prevalent, and for people living with advanced cancer in rural areas of Canada. It is a face-to-face and tele-supported non-pharmacological intervention that aims to work in collaboration with patients, families, professionals, and communities to promote quality of life and wellbeing, reduce health-related suffering, support empowerment and social engagement, and improve timely and equitable access to health and social care services and resources as needed, throughout the care and illness continuum.

Nav-Care was originally modelled based on the evidence from cancer navigation studies showing navigation is effective in improving cancer treatment and the principles of an early supportive or palliative care approach,[14] followed by a culmination of collaborative research work across Canada. This work entailed the conceptual and theoretical foundations for navigation; creating, testing and refining a curriculum for navigators; conducting several pilot studies to determine feasibility and acceptability of Nav-Care, as well as knowledge translation studies, and mixed methods evaluations. Originally, the Nav-Care intervention was nurse-led but later adaptations involved volunteers as navigators.[14,26,29,30] The intervention has proven its feasibility in different contexts in Canada, including rural communities; has been implemented in 27 sites in 6 Canadian provinces and is currently being scaled-up in 30 additional sites throughout Canada with the support of Health Canada. Recent mixed-method evaluations[14] showed patients were highly satisfied with the intervention, citing benefits of social connection and support, help with negotiating the social aspects of healthcare, better knowledge of services available to them and access to cost-effective resources, and family

respite, all factors that contribute to people's quality of life and wellbeing. The SF-12v2 health survey – measuring functional and mental health, validated in the general population – was used as a proxy for quality of life, and SF-12v2 scores remained stable over time. However, quality of life and wellbeing in serious illness are broad concepts that entail more dimensions than measured by the SF scale,[31] hence multidimensional quality of life and wellbeing-measures validated in populations with serious illness are more appropriate outcomes to evaluate navigation interventions. High-quality research designs such as pragmatic randomized controlled trials or studies using a control group have not been used to evaluate Nav-Care. Hence, despite the reported benefits of the Nav-Care intervention and its potential to improve quality of life and wellbeing for older cancer patients and their family caregivers, it needs yet to be adapted and evaluated in European health care systems, using high-quality research designs and measurements. We require further evidence regarding its 1) effectiveness, and cost-effectiveness in Europe compared to currently provided standard cancer care in the respective countries where the intervention is implemented, and 2) evidence on how the interventions will work when integrated in different EU healthcare systems and for different subgroups of patients.

1.2. Objectives

The overall aim of this project is to implement a patient- and family-centred navigation intervention (NavCare-EU) for older cancer patients across the continuum of supportive, palliative, and end-of-life care, and evaluate its effectiveness for patients, families and care providers, its cost-effectiveness, and its implementation processes in different health care systems in Europe.

Specific objectives

a. To compare the NavCare-EU intervention to care as usual, in terms of its:
    a. effectiveness on (1) global health status/ quality of life, and the levels of social support (two co-primary outcomes); and on feelings of loneliness of older persons with cancer across the continuum of supportive, palliative, and end-of-life care; (2) caregiver burden of the family caregivers (WP3)
    b. cost-effectiveness (WP4)
    c. effects on different subgroups defined by characteristics known to affect health equity and equitable access, i.e., gender, age, socioeconomic status, extent of social support and living situation, and geographical location (rural vs. urban) (WP5)
    d. effectiveness and cost-effectiveness in different health care systems and care regimes in Europe (WP2-5)
b. To evaluate the implementation processes of the NavCare-EU intervention and the feasibility of its integration into different health care systems and care regimes in Europe, the contextual barriers and facilitators for effective and sustainable implementation, and the mechanisms involved in reaching the outcomes in each country, as perceived by patients, family caregivers, and care providers (WP6)

1.3. Trial design

This project will conduct an international 6-country multisite pragmatic fast-track randomized controlled trial (RCT) with an embedded process evaluation to compare the NavCare-EU intervention in addition to standard care with the provision of standard care alone. The trial is a superiority parallel-group trial with a 1:1.08 allocation ratio for Belgium (Flanders), Italy, Ireland, The Netherlands, and Portugal and a 1:1.45 allocation ratio for

Poland. In designing the trial we have followed PRECIS-2 guidance for designing clinical pragmatic trials and recommendations of the European Organisation for Research and Treatment of Cancer (EORTC) on clinical trial methodology on older individuals with cancer.[3] A mixed-methods process and implementation evaluation is embedded in the RCT, guided by the UK MRC Framework for complex intervention evaluation[32] and state-of-the-art implementation science frameworks CFIR [36] and RE-AIM[37].

RCTs have been conceptualized on a continuum from more pragmatic (effectiveness trials, asking "can this intervention work under usual conditions?") to more explanatory (efficacy trials, asking "can this intervention work under ideal conditions?".[28,33]) While explanatory trials serve to confirm a physiological or clinical hypothesis, the purpose of pragmatic trials is to inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice.[33] To design this pragmatic trial we have used the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) guidance, a tool containing nine domains reflecting trial design decisions that determine that trial's position on the continuum from pragmatic to explanatory.[28] Fast-track RCTs have been specifically developed and used in palliative care research.[35] They compare an intervention group against a control group until the primary endpoint is measured (i.e., 6 months in our study; see Figure 2). After this period, the control group is also offered the intervention. The design is adapted from a 'wait-list' design (sometimes called a deferred entry or delayed intervention trial) but is called fast-track as patients are not on waiting lists and because the service is usually not offered to them at all.[33] An important advantage of fast-track RCTs is that all eligible participants can receive the intervention while the RCT remains rigorously controlled. This design can also help counter patients' and families' reluctance to be randomised to a control group that is not receiving a service.[34] It can be used with patients with longer or shorter (i.e. several weeks) survival periods.[35]

For the process evaluation, quantitative and qualitative data will be collected in each country looking at the perspective of all participants to study how the NavCare-EU intervention 'works' in real-world context with a view to maximizing the feasibility of its implementation in different countries. The process evaluation will be guided by the UK MRC guidance for process evaluations of complex interventions with attention for context, implementation and mechanisms of change, integrating the Consolidated Framework For Implementation Research (CFIR)[36] that offers an overarching typology to promote implementation theory development and verification about what works where and why across multiple contexts, and the RE-AIM framework[37] which focuses on evaluating a program's Reach, Effectiveness, Adoption, Implementation and Maintenance (5 domains that interact to determine the overall impact of a health intervention program).

CFIR can be used to help guide formative evaluations of interventions in context and offers an organizational framework for synthesizing and building knowledge about what works where, across multiple settings. The CFIR comprises five major domains (the intervention characteristics, the outer setting, the inner setting, characteristics of the individuals involved, and the process by which implementation is accomplished). These domains interact in rich and complex ways to influence implementation effectiveness.[36]

RE-AIM is a framework to guide the planning and evaluation of programs according to the 5 key RE-AIM outcomes: Reach, Effectiveness, Adoption, Implementation, and Maintenance. Reach (R), Effectiveness (E), and Maintenance (M) operate at the individual level (i.e., those who are intended to benefit). Adoption (A), Implementation (I), and Maintenance (M) focus

on staff and setting levels. Setting-level RE-AIM factors are often multi-level and address context and external validity issues important to population impact. For example, settings may include clinics, schools, or worksites nested within communities or larger systems, and within these settings are nested clinicians, teachers, or human resources staff responsible for implementation. Implementation (I) focuses on fidelity to an intervention: the extent to which the program is implemented consistently across different settings, staff, and patients. It also includes adaptations made and costs from multiple stakeholder perspectives.
Maintenance (M) has indices at the individual- (long-term effectiveness) and setting-level (sustainability after original research funded is completed)[37].

This pragmatic RCT will be conducted in six European countries. The present study protocol describes this general framework of the RCT but focuses on the specific methods and procedures as they will be conducted in country X, for the purpose of the application to the commission for medical ethics. Our partners in the other countries will apply with their respective ethics committees for the parts of the RCT that will be conducted in their countries. Belgium is the coordinating partner of EU NAVIGATE.

2. Methods

2.1 Participants, interventions, and outcomes

2.1.1 Study setting

The RCT and process evaluation will be conducted in Belgium (Flanders), Ireland, Italy, the Netherlands, Poland, and Portugal. The selection of countries was based on achieving good variation in healthcare systems characteristics and socio-cultural factors. Within each country, the intervention will be implemented in real practice as this is a pragmatic trial.

In Belgium, two implementation sites will be involved in implementation of the intervention (in Flanders, the Flemish-speaking part of Belgium), one palliative care network and one primary care network (both in different geographical regions). In each site, one organisation will engage a "navigator coordinator" (see intervention description for details), who will collaborate with other organisations within their own regional primary care network or municipality and with the researchers and trainers to train volunteers to deliver the intervention to patients and families.
In the Netherlands, two implementation sites will be involved in implementation of the intervention (in the province Noord-Holland of the Netherlands). Each site will engage a "navigator coordinator" who will collaborate with the researchers and trainer to train and mentor volunteers to deliver the intervention to patients and families.

In Ireland, a maximum of one site will be involved in implementation of the intervention (Tertiary hospital St. James's Hospital, Dublin). We will engage volunteers from the Irish Cancer Society. Palliative care organisation: Our Lady's Hospice Harold's Cross The Trinity St James's Cancer Institute.

In Poland, navigators will be employees from the Polish partner and will have an educational background in social work. They will be coordinated by a navigation coordinator and trainer. Poland will not work with volunteers. Implementation site is the region of Krakow.

In Portugal, one implementation site is involved (in Coimbra, which is located in the Centre Region). They will recruit participants via one clinical site (Portuguese Institute of Oncology of Coimbra) and will allow referrals from the community. They will engage volunteers from the Portuguese League Against Cancer – Centre Region, who will be trained and coordinated by "navigator coordinators" employed by the UC and jointly supervised by the UC and the Portuguese League Against Cancer – Centre Region.

In Italy, the implementation is set to take place in the Milan city area, Hinterland, and Monza Brianza, in Lombardy region. The project will be overseen by a navigator coordinator, country trainer, and project manager, who will work with various social services, municipalities, and non-profit associations to provide support to elderly cancer patients. In addition, the project will collaborate with several cancer facilities and foundations in the Milan region to ensure that all patients have access to high-quality care. The intervention will be delivered to patients and their families by trained volunteers, who will be trained by the country trainer and project manager. This initiative aims to improve cancer care in the Milan region and provide much-needed support to older cancer patients and their families.

2.1.2. Participants and eligibility criteria

In this pragmatic trial, and in line with recommendations for cancer trials in older populations,[17] the eligibility criteria are formulated to include typical individuals who would use this intervention if it were implemented in current practice. Therefore, recruitment and eligibility criteria correspond to those that would be used if this intervention were part of usual care, i.e. they are broad and include a wide range of settings from which potential participants will be recruited. This corresponds to guidance for pragmatic trials.[28]

The inclusion and exclusion criteria are presented in Tables 1 and 2. Regarding the close family caregiver, only the one who lives with the person with cancer or provides care at least on a weekly basis**,** and who is identified as the primary family caregiver by the person with cancer, will be eligible for inclusion. The family caregiver can be a family member or relative but also a friend without blood relationship. In case a person with cancer does not have such a close family caregiver, s/he is eligible to be included without a family caregiver. If the patient has other caregivers, these are not part of the evaluation in this trial. If there are multiple caregivers, the patient will decide who would be the best person to involve.

Table 1. Inclusion and exclusion criteria for older people with cancer

Inclusion criteria
Have a cancer diagnosis (active cancer, meaning not being cancer free, of any stage and involving any treatment/care regimen; i.e. curative, life-extending, or palliative), AND
Aged 70 years or over*, AND
Have declining or deteriorating health using the Clinical Frailty Scale**, AND
Live at home (own home or home of the family caregiver) (or discharged home if recruited in hospital), AND
Live within the catchment area of the navigation programme/service
Exclusion criteria
The close family caregiver living with the person with cancer or providing care at least on a weekly basis, and identified as the primary family caregiver by the person with cancer, *if present*, does not agree to participate in the study (unless participation is explicitly requested by the patient) , OR
Lives in a care or nursing home, or is incarcerated, OR
Currently receives care from a formally recognized community-based multidisciplinary or specialist palliative care team***, OR
Is unable to provide informed consent or has difficulties understanding the information about the study ,

OR
Has a psychiatric condition (i.e. schizophrenia, bipolar disorder, or major depressive disorder) or has an active substance abuse disorder
Is not able to participate in data collection in the country's language

**Following EORTC reference point for older cancer patients*
*** The Clinical Frailty Scale (CFS) will be used to determine whether the patient has declining or deteriorating health. More specifically, declining or deteriorating health means at least 1 change in CFS score ending in score 4 in the last 6 months, OR everyone scoring 5 or higher.*
**** i.e. services whose main task is to provide palliative care (e.g. in Flanders, multidisciplinary palliative home care team, admission to palliative care unit).*

Table 2. Inclusion and exclusion criteria for close family caregivers of people with cancer

Inclusion criteria for close family caregivers (if present)
Aged 18 years or over , AND
Lives with the person with cancer OR provides care at least on a weekly basis, AND
Identified as primary family caregiver by the older person with cancer
Exclusion criteria
Is unable to provide informed consent or has difficulties understanding the information about the study, OR
Is not able to participate in data collection in the country's language

2.1.3. The NavCare-EU intervention

Concepts, models and assumptions underpinning the EU NAVIGATE intervention

The Nav-Care© intervention: conceptual model and core components

The navigation intervention for older people with cancer and their family caregivers is conceptually based in the Nav-Care© intervention developed and successfully tested in Canada by Pesut and Duggleby (henceforth called Nav-Care).[14,26,27,29,30] Nav-Care is a person- and family-centered navigation intervention, aimed at improving quality of life and wellbeing throughout the care and illness continuum, via the involvement of a patient/family navigator. Navigation is working in collaboration with patients, families and communities to connect them with appropriate resources, information and others to promote quality of life, support independence and facilitate community connections. A family centric, cultural humility, and palliative approach is used.

The **intervention's conceptual model outlined in Figure 1** shows the core intervention components, how they work to impact patients' and family carers' outcomes and which contextual and patient/family characteristics can influence the implementation of the intervention and its outcomes. As the intervention is a complex intervention operating within a health care system, we used guidance from a previous EU-funded project, INTEGRATE-HTA,[38] to create a logic model or a graphic description of how Nav-Care works, which will also be used guide our outcome and process evaluation. **Nav-Care is a free program**; the copyright concerns the need to acknowledge the original developers of the intervention and the expectation to implement the program with a high level of quality and consistency.

Core components of Nav-Care © (see Figure 1 and Table 3)

Navigators collaborate with patients and family caregivers throughout the continuum of supportive, palliative, and end-of-life care. Their main activities focus on connecting clients to social supports, both formal and informal, advocating for clients in meeting their quality-of-life goals, resourcing by identifying needs and negotiating access to meeting those needs, and engaging clients in what is most meaningful to them. Above all, navigators are trained to ask the question 'What is most important to you today?' and work alongside patients and

families to help them accomplish that. Navigators are selected, trained, and mentored volunteers or professionals (licensed or unlicensed) (depending on the best fit with the health care context of the country or region of implementation). They have **face-to-face and/or telephone or IT-supported** contact with patients and family carers, every two weeks on average or in different intervals, as needed. Nav-Care has a clear and specific implementation model. Navigators are matched to patients and family carers by **navigator coordinators** who are also responsible for championing the intervention and for networking with and connecting to health and social care professionals in the community and in hospitals in the region. Navigators and coordinators are trained, coached, and mentored by a **navigation trainer** (someone from a nursing or other healthcare background and experience in palliative or supportive care) and trainings are competency-based and blended (14 hours of training at the start + monthly coaching sessions). The **Nav-Care Toolkit** (Table 3) supporting the implementation contains blended (part online, part in-person) training and implementation tools and manuals.
Nav-Care was designed to enhance, not replace, professional health and social care in the region where it is implemented and to be responsive to the individual needs and wishes of patients and families. While it has several defined core components, the intervention is highly adaptable, and should be tailored to individual patient and family needs and local contexts while retaining its core components and hence its functional integrity.

From Nav-Care© to NavCare-EU
Nav-Care© will be translated and adapted from Canadian to the EU context –specifically to each countries' care context and populations of older cancer patients– into a **standardized European NavCare-EU intervention** for implementation and evaluation in 6 EU countries. Adaptations will be done using user and stakeholder engagement (following ADAPT guidance[39]), but without compromising the functional integrity of the intervention as a whole, i.e. the extent to which the core functions and processes (core components) of the evidence-based intervention are maintained. The translation and adaptation process are described in Appendix 1.

International component
To support implementation in the 6 countries, **country trainers** will be appointed, trained, mentored and coached on a regular basis (monthly or as needed) by the original developers from Canada (P7) together with a trainer from P6 (i.e. **International Trainers)**. Training will be competency-based, blended, and uses a Train-the-Trainer approach. International trainers will aid country trainers to implement the intervention in their specific healthcare contexts and address country-generic and country-specific barriers and facilitators.

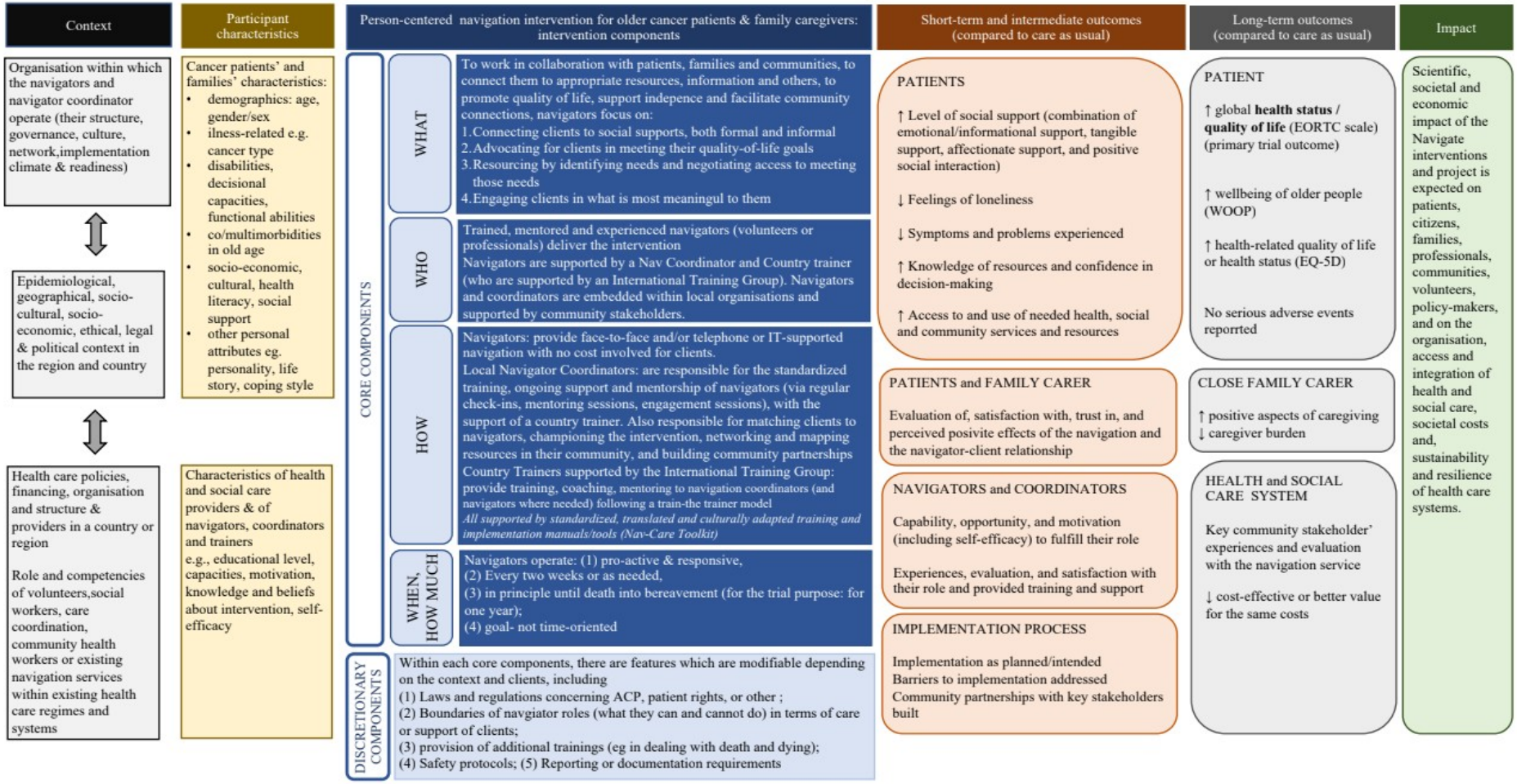
Table 3 Tools of Nav-Care© translated and adapted to the EU context

Tool	Aim and format	Used by
a) Training & manual for country trainers using Train the Trainer approach	- to assist country trainers with the delivery of education, coaching, training and mentoring for navigators and navigator coordinators. - a combination of online and in-person training to apply the knowledge, supported by a train-the-trainer manual and manuals b) c) and d)	Country trainers
b) Navigation coordinators' training and manual	- to assist navigator coordinators with the successful implementation of the navigation program in their community/region - a combination of online and in-person training to apply the knowledge, supported by a navigation coordinator Manual - including a community resource template to map all resources available to patients/families in the region	Navigation Coordinators
c) Training for navigators*	- covers all information and tools needed to become a navigator - a combination of competency-based online and in-person training to apply the knowledge, supported by a Navigators' Learning Manual	Navigators
d) Implementation manual for organizations	- to help organizations to implement the Navigation program, ensuring a good fit between the goals of the program and the vision of the organization, and to help with drafting sustainability plans	Organizations implementing
For the international implementation, the NavCare-EU Toolkit will additionally include:		
e) international blended training using Train the Trainer Approach	- to assist international trainers with delivering training for country trainers - a combination of competency-based online and in-person training to apply the knowledge supported by the manuals and tool of NavCare-EU	all implementation partners

*Topics Navigator training manual:

- *Addressing quality of life concerns (module 2)*
  - Identify values and beliefs regarding quality of life
  - Determine priorities for quality of life
  - Support decision-making toward quality-of-life priorities
- *Advocating for clients and families (module 3)*
  - Identify needed resources
  - Identify barriers to accessing needed resources
  - Advocate to overcome barriers to needed resources
  - Advise on negotiating for resources
  - Facilitate self-navigation toward desired level of independence
- *Facilitating community connections (module 4)*
  - Identify and assist with accessing community resources
  - Determine best fit with available resources
  - Identify gaps in available resources and navigate alternative options
  - Assist to connect or reconnect with social networks
- *Promoting active engagement (module 5)*
  - Identify and/or develop opportunities for meaningful engagement
  - Build capacity toward desired level of engagement
  - Facilitate discussion about future planning
  - Promote engagement in decision-making
- *Supporting virtual navigation (module 6)*
  - Determine best practices for virtual navigation
  - Build capacity for virtual engagement
  - Assist with self-navigation in virtual environments
  - Provide virtual navigation

Figure 1 presents the conceptual model with core components of the foreseen NavCare-EU intervention after adaptation from the Canadian NavCare intervention.



Pilot-testing of the NavCare-EU research procedures

We will perform a small-scale pilot testing to test the research procedures, maximize feasibility of the study, and troubleshoot issues that arise during set up of the implementation. The pilot study will be performed using **five fictional cases** of patients and family caregivers, carried out as roleplays by researchers and data collectors in each country (hence, the pilot study will not involve real patients or family caregivers). Each case will demonstrate a unique situation that might occur during recruitment and/or data collection, and is used to train the data collectors, and researchers.

Participants: The role play of the patient and researcher/data collector in the fictional cases will be performed by members of the research team (and of the implementation team if a country desires so). Members of the research teams in each country will divide the different roles, so everyone is able to perform the role that he/she will have in the actual trial at least once.
Content and procedure: The members of the research team will in each of the cases be asked to contact the patient and/or family caregiver, perform the eligibility check, explain the study to the patient and family caregiver and ask for their informed consent, performing baseline measurements, perform the randomisation, and inform the patient and family caregiver of the study arm to which they are randomised (immediate start of the intervention or delayed start). The five case descriptions are varied so that researchers and data collectors can practice all research procedures and possible exceptions.
The roleplays will be a part of the researchers/data collectors training.

Data collection: . A member of the research team will enter the data obtained from the fictional cases/role plays in RedCap[40] to test the data collection and data entry procedures, including randomisation via this online system. This data will be deleted after completion of the pilot study and before the start of the main trial.

Outcomes of this pilot: Once all five roleplays are carried out in each country, the researchers are asked to complete a country report highlighting any arising issues, questions and suggested adaptations to the research procedures where necessary. Any experience that may involve modifications to the research procedures will need to be reported to the coordinator VUB. The country reports are collected and analysed by the coordinator VUB who is WP3 lead. Final decisions regarding adaptations to the research procedures are made at the level of the consortium during one of the international WP research meetings, as well as the decision to start the main trial. No country can initiate the main trial without the formal agreement of the coordinator. Major changes to the study procedures may require requesting amendments to local ethics committees.

Timing: The researchers/data collectors in all countries will be given one month to complete the pilot study. The report of the pilot study should be completed by September 2023, so that all countries can start with the main trial in October-November 2023 .

Control (non-fast track) group (care as usual)

All patients will receive what is usual care in each of the participating countries. In pragmatic trials, i.e. when implementing a new intervention in the 'real world', it is important to describe usual care in sufficient detail.[33,41] In preparation of this proposal, we have described (for each country): 1) the type of health care system; 2) current organization of cancer care regimes in terms of laws and regulations, specifically concerning pain management, supportive and survivorship care for cancer patients in general and for older cancer patients in particular; 3) current integration of palliative and end-of-life care within oncology regimes; 4) current navigation models in the country or region, if any. This will be updated prior to trial start, for future reference and reporting.

Criteria for discontinuing or modifying allocated interventions

When a patient or included family caregiver dies during the study period, a bereavement protocol will be in place. The national trial manager will be notified about the death of a participant by either the navigator coordinator or research assistant/researcher who should be informed about this when trying to make an appointment with the participant for data collection. The bereaved participant will be able to inform the national trial manager about the death of their relative themselves via e-mail or phone. The bereaved participant will receive a phone call from the navigator outlining condolences and the options for where they can access support (relevant to each country) if required and what the implications are for the study. If the bereaved person seems very distressed, the navigator can offer to call the person a second time (e.g., one week later) to determine that the person has contacted a source of support (e.g., family, clergy, physician, bereavement group). In case the older person with cancer dies, the intervention and data collections will end for this person and their family caregiver, and the researcher will document that the patient has died. In case a family caregiver dies, the bereaved older person with cancer will be asked to continue to participate in the intervention and data collections. Any other reasons for discontinuing the interventions are described in the informed consent (participants can withdraw from the study at any moment) or under the section of adverse events (such as psychological distress).

Relevant concomitant care and interventions that are permitted or prohibited during the trial

There are no restrictions regarding concomitant care during the trial outside of the trial arms.

2.1.4. Outcomes (outcome, cost-effectiveness, and process evaluation)

PRIMARY ENDPOINTS

The **two co-primary endpoints** for the EU-NAVIGATE trial are (1) the older person with cancer's **global health status/quality of life** and (2) the **levels of social support as reported by the older person with cancer at 24 weeks** (T2). The global health status/quality of life is a 2-item subscale from the EORTC-QLQ-C30 (revised) measuring health-related quality of life[42]. The levels of social support (i.e. emotional/informational support, tangible/instrumental support, positive social interaction, and affection) will be measured with the Medical Outcomes Study Social Support Survey (MOS).[43]

The statistical tests for the two primary outcomes will be adjusted for multiple testing. The NavCare-EU intervention will be considered as beneficial if statistically significant and clinically relevant superiority can be demonstrated **on at least 1 of the 2 outcomes**.

The primary endpoints were chosen based on the **logic model** of the NavCare-EU intervention (Figure 1). We choose one distal outcome (global health status/quality of life) and one intermediate outcome (levels of social support) of the EU Nav-Care intervention programme. We decided to measure the primary endpoint at 24 weeks with a view to allowing sufficient time for the NavCare-EU intervention to have an effect and to ensure sufficient retention of participants for follow-up measurements (estimates based on previous Nav-Care studies[14,26,27]; see also sample size section for details).

SECONDARY ENDPOINTS

The **secondary endpoint for the older person with cancer**, measured **at 24 weeks (T2)**, is:
Feelings of loneliness (relational and social connectedness, and self-perceived isolation)

A secondary endpoint for the family caregivers (if present) is caregiver burden and positive aspects of caregiving and is measured at 24 weeks.

TERTIARY OR EXPLORATORY OUTCOMES (moderators and mediators)

We will analyse as tertiary outcomes the constructs measured as primary and secondary outcomes at 48 weeks and 72 weeks (people with cancer and family caregivers) to analyse whether the effects of NavCare-EU on the primary and secondary endpoints change over time and whether receiving NavCare-EU earlier or later has a different effect on the primary and secondary endpoints.

Additionally, we will collect several **exploratory outcomes** to assess potentially moderating or mediating factors between intervention and outcomes, and several measures for the **cost-effectiveness evaluation** of the intervention.

We will measure the following tertiary outcomes among patients (see figure 1):

- symptoms or problems experienced (i.e. as measured by the EORTC-QLQ-C30 symptom subscales and the emotional functioning scale for cancer patients
- well-being of older people (WOOP) (which captures a comprehensive set of well-being domains relevant to older people (broader than health) (can also be used as outcomes measure in economic evaluations as one of the newly developed measures);

Table 5. Constructs measured in the study and corresponding instruments

Constructs	Measures	Items	Timing				
			T0 (baseline)	T1 (T0 + 12 weeks)	T2 (T0 + 24 weeks) Primary endpoint	T3 (T0 + 48 weeks)	T4 (T0 +72 weeks; control group only)
Primary outcomes at 24 weeks							
Older person with cancer							
Global health status /quality of life	EORTC QLQ-C30 (version 3.0): global health/quality of life scale	2	✓	✓	✓	✓	✓
Levels of Social support	Medical Outcomes Study Social Support Survey	19	✓	✓	✓	✓	✓
Secondary outcomes at 24 weeks							
Older person with cancer							
Feelings of Loneliness	3-item-UCLA Revised Loneliness Scale.[41]	3	✓	✓	✓	✓	✓
Family caregiver							
Caregiver burden	Zarit Burden Interview Short Form	12	✓	✓	✓	✓	✓
Exploratory outcomes / potential mediators or moderators of intervention effects							
Older person with cancer							
Perceived health-related quality of life and symptoms or problems experienced (i.e. physical, role, emotional, cognitive, and social functioning as measured by the EORTC-QLQ-C30 for cancer patients	EORTC QLQ-C30 (v 3.0) emotional functioning scale and symptom scales	12	✓	✓	✓	✓	✓
Well-being of older people	WOOP	9	✓	✓	✓	✓	✓
Knowledge of resources and services and confidence in decision making	Items from Patient Engagement Survey Canada	8	✓	✓	✓	✓	✓

Health status	EQ-5D	5	✓	✓	✓	✓	✓
Health and social care services and resource use	Adapted Client Services Receipt Inventory*		✓	✓	✓	✓	✓
Family caregiver							
Health status	EQ-5D	5	✓	✓	✓	✓	✓
Positive Aspects of Caregiving	Positive Aspects of Caregiving (PAC)	10	✓	✓	✓	✓	✓
	Independent variables and subgroup descriptors for patients and family caregivers (socio-demographics)						
Socio-demographic & clinical characteristics		Client: 17 Carer: 13	✓				

- Knowledge of resources and services and confidence in decision making and communicating those decisions (measured with the Nav-CARE engagement questionnaire).
- Health status EQ-5D (has traditionally been used as outcome measure in economic evaluations)
- Health and social care services and resource use (for economic evaluation)

We will measure the following tertiary outcomes among family caregivers (if present):

- positive aspects of caregiving

OTHER SOCIO-DEMOGRAPHIC AND CLINICAL MEASURES

We will assess sociodemographic and clinical information of the older person with cancer and the family caregivers.

MEASUREMENT INSTRUMENTS

We will use established and validated measures to assess all outcomes. Table 5 provides an overview of all constructs assessed and questionnaires used. The questionnaires can be found in Appendices 4 and 5.

Methods used to enhance the quality of measurements

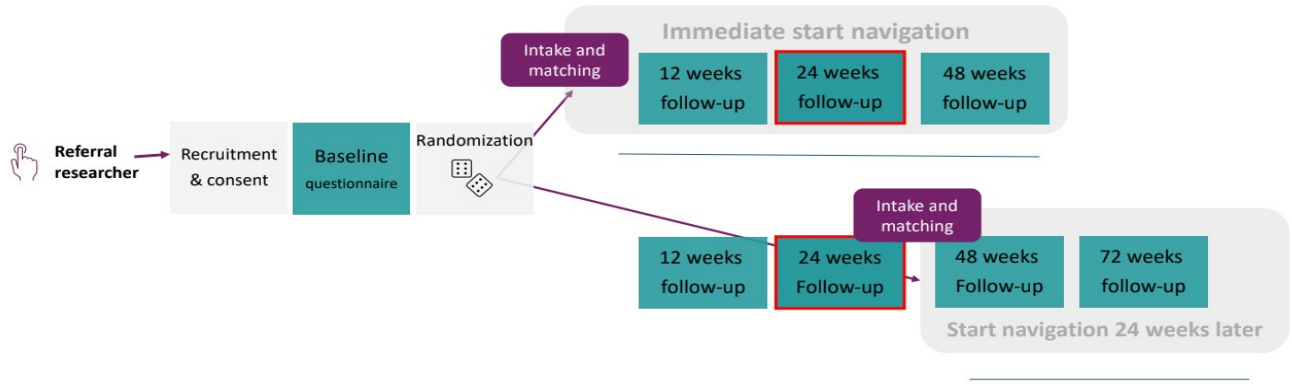
All questionnaires were translated in the participating countries' languages and feasibility-tested with around 6-10 experts from the countries' Local Adaptation and Research Teams, composed to adapt the Nav-CARE intervention to the country context as part of WP2 (see Appendix 1). This testing of the questionnaires included testing that the items and response scales were well understood by respondents, that questionnaires for self-completion were readable and clear, and that the whole of the measurements do not exceed an acceptable amount of time (approx. 30-60 minutes, based on experience with previous trials among older people in poor health). The feasibility tests of the measurements were conducted through cognitive interviewing of respondents while they completed the measurements. The procedures followed for the translation and feasibility testing of the questionnaires are described in detail in a Quality Assurance Manual.

2.1.5. Participant timeline

Figure 2 shows the time schedule of enrolment, interventions, assessments, and visits for participants.

Potentially eligible patients and their close family caregivers (if present) are identified and referred to the researcher by professionals and organisations. For all patients (and family caregivers) who are potentially eligible, researchers will perform eligibility screening and ask the patients and family caregivers for informed consent before inclusion in the study. After inclusion, participants will take part in the baseline measurements. Immediately after the baseline measurement, participants are randomized to either group 1 or group 2. Group 1 will start with the navigation intervention as soon as possible and will have a 12 weeks, 24 weeks (primary endpoint) and 48 weeks follow-up measurement. Group 2 will start the navigation 24 weeks (primary endpoint) after randomization and will have follow-up measurements at 12, 24, 48 and 72 weeks.

Figure 2. Participant timeline



2.1.6. Sample size

To achieve at least 80% power to detect a mean difference between groups of 10 points in patient's global health status/quality of life using an analysis of covariance (ANCOVA) adjusted for baseline global health status/quality of life, at the two-sided 2.5% significance level assuming a standard deviation of 25 points and a correlation of 0.3 between baseline and 24 weeks, a total sample size of 220 patients is needed with a balanced design (allocation ratio 1:1). Taking into account the partially nested study design (there is only a cluster effect of navigators in the intervention group), 115 patients in the control group and 131 patients in the intervention group is most efficient, assuming on average 1.5 patients per navigator in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal (recruiting 5/6 of all patients), and 10 patients per navigator in Poland (recruiting 1/6 of all patients), and an intra-cluster correlation (ICC) of 0.10. Anticipating a drop-out rate equal to 50% (17.5% due to mortality, 32.5% due to other reasons),

229 subjects in the control group and 260 subjects in the intervention group are needed (total sample of 489, of which 81 patients from Poland and 83 patients from the other countries).
The sample size calculation was performed using SAS software (version 9.4) and is based on the paper from Moerbeek and Wong (2008).
The sample size calculation is based on the following assumptions:

1) A mean difference between groups of 10 points is considered the smallest clinically relevant difference in the mean score of EORTC QLQ-C30.
2) The standard deviation of 25 points reflects the heterogeneity in the score at 6 months in EORTC QLQ-C30 in a similar usual care population (EORTC Quality of Life Group, 2008).[44]
3) An ICC of 0.1 was chosen as a conservative estimate as there is currently no empirical data to support an exact estimate of the ICC.
4) A correlation between baseline and 24 weeks in baseline global health status/quality of life of 0.3 was chosen as a conservative estimate considering that correlations for longitudinal measures are very rarely below 0.5.
5) A drop-out of 50% is a more conservative estimate than those reported in the Nav-Care feasibility and pilot studies (35% over 1 year[26], 40% over 1 year[14], 17% over 6 months[27]). Moreover, the final analysis will include the available information from patients who drop out.
6) A significance level of 2.5% was chosen to control the Type I error rate, because the trial is designed so that two study endpoints could lead to a conclusion that effectiveness is established (Bonferroni correction).

We estimate an enrolment rate (patients enrolled out of all deemed eligible) of 55%. This includes an estimated 10% not being eligible because the family caregiver does not agree to participate, based on a palliative care pilot RCT in older people conducted by P1 VUB.[46] **This means we estimate to approach 151 patients per country in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal to enrol 83 and 148 patients in Poland to enrol 81**

2.1.7. Recruitment

Pragmatic trials typically aim to recruit broader groups of patients from a variety of settings to represent all who may benefit from the intervention should it be implemented in standard care.[28] Hence, we will recruit participants from a range of settings where patients from the target population receive care/support (i.e. hospitals, community or volunteer organisations).

Each country has a recruitment strategy in place, aimed to achieve enrolment of the targeted sample size into the pragmatic RCT (see sample size calculation in section 2.1.6) and aiming to recruit a diverse the sample in terms of age, gender, cancer diagnoses, cancer care regime (curative or non-curative/no treatment), education as proxy for socio-economic status (higher vocational training or university versus lower education), and living situation as proxy for aspects of social vulnerability (eg. also participants living alone).

Recruitment will run over 12 months or until the targeted sample size is achieved.

Recruitment strategies to obtain these recruitment objectives involve the following:

- **Establishing close partnerships** with local stakeholders such as hospitals or community organizations within the region where the intervention is rolled out. These partnerships have partly already been set up and will be further developed throughout the trial period as part of the key tasks of the navigator coordinator. Specifically with regard to Ethics approvals, recruitment via hospitals will usually need an additional ethical approval by the local Ethical Committees, which researchers will ensure to obtain next to obtaining approval from their own central Ethical Committees.
- **Targeted efforts to recruit from a diverse population including people in socially vulnerable positions**[1]. Indicators for social vulnerability can be for instance financial circumstances (e.g. low income, being 'outside of the employment market', receiving unemployment-, sickness- and/or other social benefits or early retirement pension), communicative resources (e.g. low educational status qualified or signaled by lack of communicative resources, difficulty reading and understanding information, limited proficiency in the country's language), social contexts (e.g. limited social network including being single or living alone, loneliness, 'burdensome' family circumstances, unstable housing), health-related issues (e.g. multimorbidity and disability, mental health problems, current or previous substance abuse), personal resources (e.g. lack of trust in health and social care system). Each local implementation site will further operationalize these efforts as part of the implementation of the intervention programme (led by the local navigation coordinators). This might for example concern setting up collaborations with local stakeholder groups that have focused their work on specific populations and asking for their participation.
- **Monitoring** the number and characteristics of patients recruited into the study per country on a regular basis (i.e. monthly per country and every three months across the six countries taken together). This information will be monitored by the coordinator VUB using the online service REDcap (Research Electronic Data Capture). VUB will initiate contingency plans if recruitment is too slow or if sample is insufficiently diverse, e.g. discussion with partner who is slow with recruitment what possible additional recruitment efforts could entail, setting up a learning network with the consortium of all trial managers to improve recruitment, discuss within the consortium what solutions might be.

Recruitment procedures:
Depending on the recruitment setting, potentially eligible patients and their close family caregivers (if present) will be identified via different professionals and organisations, including oncologists or geriatricians in hospitals, primary care physicians, home care nurses, social workers in the community, and community or voluntary organisations (see implementation strategy of the intervention programme). Those identified by professionals may be people whom they see in person (e.g. during a hospital admission or in consultations), but it can also be potential participants identified through patient/client lists. For all patients (and family

[1] There is no agreed-on definition or conceptualisation of social vulnerability in cancer care, and diverse terms have been used to designate relevant populations, such as social position, social marginalisation, social class and social vulnerability. In this study, we use the term social vulnerability as it encompasses the potential effects of a wider range of influences, including socioeconomic, but also health-related, social and other personal resources. The concept of social vulnerability also acknowledges that the vulnerability and risk of poor health outcomes lies not only in the individual person but also in their interaction with a healthcare system that is more or less adapted to their specific needs.[47] Furthermore, it has been argued that social vulnerability is not a static characteristic, but should be thought of as layered, dynamic, relational and contextual.[47]

caregivers) who are potentially eligible, researchers will need to perform eligibility screening and informed consent before inclusion in the study. This will guarantee the correct research procedures are followed.

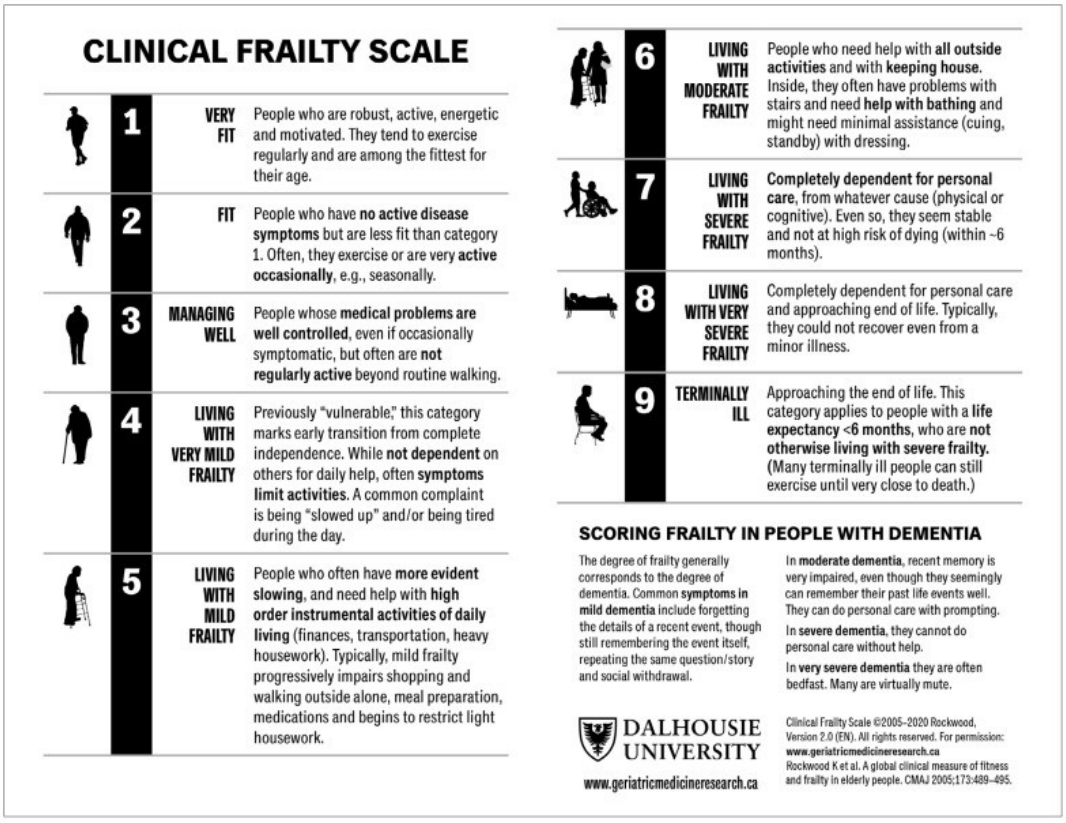
The researchers will follow different ways of approaching potential participants to inform them about the study, depending on the route of referral/identification:

1. **Referral by health or social care professional following in-person contact:** Once a potentially eligible participant (and his or her close family caregiver, if present) is identified, they will first be approached concerning study participation by the relevant professional who will ask them if a researcher may get in touch with them to explain the study to them, check eligibility criteria, and explore whether they are interested in participating. If they agree, they will be contacted by a researcher who will explain the study and conduct a thorough eligibility screening. This contact may occur in person, by phone, or videocall, depending on the potential participant's preference.
2. **Referral by health or social care professional and contact from patient/client lists is an additional referral route, particularly for those countries or sites where recruitment of patients is foreseen to be challenging:** The relevant organisation/professional will mail (e-mail or regular post) a study information sheet to potential participants that will be provided by the research team, with a short explanation of study aims and target population and announcing that a researcher will get in touch with them in the following month (see Appendices 4 and 5). We will follow an opt-out method, whereby the information sheet will invite the recipient to notify the relevant organisation/professional if they do not wish to be contacted by a researcher. If no rejection is received within 3 weeks, the research team will contact the potential participant by phone to provide further information on the study, check eligibility criteria, and inquire whether they are interested in participating. This manner of contacting potential participants through an opt-out system results in higher enrolment percentages than opt-in strategies is considered ethically acceptable and has been successfully used in studies surveying older people in the community [47]
3. **Other referrals: In some countries, other referrals than outlined in 1 or 2 might occur. This will depend on the actual implementation strategy developed in each country to obtain the necessary number and diversity of patients (see recruitment aims).** If the programme is advertised widely, community or volunteer organisations might encounter potentially eligible persons in their day-to-day activities whom they would like to refer to the navigation programme, or they might be approached directly by potentially eligible persons (or their families) who show interest in the study. All these patients will need to be referred to the researchers first. Researchers (or research assistants) will contact the potentially eligible participants to explain the study to them, check eligibility criteria, and perform informed consent. This contact may occur in person, by phone, or videocall, depending on the potential participant's preference.

Eligibility screening of patients:
Eligibility criteria will be evaluated by the researchers (or research assistants) via a short interview. The criterium 'Have declining or deteriorating health' will be checked by the

researcher using the Clinical Frailty Scale (CFS) as a screening tool (see figure 3)[48]. A person will be included if there is at least 1 change in CFS score ending in score 4 in the last 6 months, or if the patient has a CFS score of 5 or higher.

Figure 3 Clinical Frailty Scale. Figure from Rockwood K and Theou O. Using the Clinical Frailty Scale in Allocating Scarce health Care Resources. Can Geriatr J. 2020 Sep; 23(3): 210-215.



All researchers and research assistants performing eligibility screening will be trained to do the interview with patients and judge their CFS score.[48] The CFS is a judgement-based frailty tool that evaluates specific domains including comorbidity, function, and cognition to generate a frailty score ranging from 1 (very fit) to 9 (terminally ill). It was originally developed for the Canadian Study of Health and Aging and has since then been widely used in multiple settings.[49] CFS is commonly used to predict health outcomes, particularly mortality, comorbidity, and functional decline. It can be easily conducted as the scale focuses on items that can be readily observed without specialist training.[48] The scale can be introduced by saying something like: "I'd like to know how you are doing overall", after which four features are surveyed ie how the person moved, functioned, thought, and felt about their health over the last two weeks. In case the patient is judged to have a score of 4, the researcher will retrospectively evaluate with the patient his/her condition over the past 6 months to judge whether the patient has been stable or not. If how to classify the person is not clear, researchers will discuss with consulting clinicians in the project. If they fit two categories equally well, in routine care it is best to score the scale at the higher or more dependent level.

Patients' abilities to provide informed consent will be determined by the researcher/research assistant using a brief questionnaire containing yes/no answers to check understanding of the study information. As cognitive function in older people can fluctuate, and may decrease over time, we will ask patients to indicate a proxy (family caregiver or other) who can be consulted regarding the patient's continued participation in the study should their cognitive abilities decline throughout the study.

For the screening of the criterion of having a psychiatric condition or an active substance abuse, the researcher will either ask the referring professional to check the medical record for any documentation of active and severe mental illness (i.e. schizophrenia, bipolar disorder, or major depressive disorder), active suicidal ideation, or active substance abuse) or ask the patient him- or herself whether such a diagnosis has been made by a professional.

When after the eligibility screening, the patient is deemed ineligible to participate in the study, the researcher will document the reasons why the patient was not eligible.

Eligibility screening of close family caregivers:
Patients will be asked whether they have a close family caregiver, defined as someone who lives with them or who provides care to them at least once a week. If there is no such family caregiver, patients will be eligible for participation in the trial on their own. If they do have such a close family caregiver, it will be necessary that both are willing and able to take part in the study. Researchers or research assistants will explain the study, perform the eligibility screening, and follow informed consent procedures for both patients and family caregivers. This can be done together (at the same time) or separately, depending on what it most practical.
As different professionals or organisations will be involved in recruitment, having the first contact with patients and families, it will be important for these professionals and organisations to understand how the recruitment procedures will be performed, how they can make a first judgement on eligibility themselves, and how to explain who is eligible for being included in the programme in lay or easily understood language. This is part of the implementation strategy of the trial (see intervention description).

Documenting the eligibility screening
The researcher or research assistant will carefully document the reasons why a patient or family caregiver is considered eligible or not. If a person is considered eligible, but does not want to participate, the researcher will document the reasons when the person is willing to share them (e.g. they do not want to be visited by a navigator). For public interest, the data of non-eligible participants will be also be registered and stored. This is only concerns the reason for ineligibility or reason for non-participation, in case participants want to share this.

2.2. Assignment of interventions

2.1.2. Allocation

- Randomization will take place after all baseline measurements have been completed.
- We will randomize patients in a 1:1.08 allocation ratio (Control:Intervention in Belgium (Flanders), Ireland, Italy, The Netherlands, and Portugal in a 1:1;45 allocation ratio in Poland. These are the most efficient allocation ratio's given the partially nested design (see sample size calculation).
- We will use permuted block randomisation with varying block sizes.
- Randomisation will be stratified by country.
- Randomisation lists will be uploaded in REDCap (Research Electronic Data Capture).[40] REDCap is a secure web-based software platform designed to support randomisation and data capture for research studies.

N.B. If, after the baseline measurements have been completed, a patient turns out not to be eligible for participation in the study after all, the patient will not be randomized and cannot take part in the study (s/he will be informed about this then).

2.1.3. Blinding

Due to the nature of the intervention which includes patients being visited by navigators, neither the older persons and their family caregivers nor the researchers/research assistants can be blinded to allocation. Data will be collected via questionnaires and interviews with a researcher or research assistant that is present for assistance and additional explanations. Those conducting the data analyses will remain blind as to what trial arm participants were randomized to.

2.3. Data collection, management, and analysis

2.3.1 Data collection methods (for outcome and process evaluation)

Informed consent will be obtained either on a pen-and-paper form through in-person contact or by posting a form to the participant together with a post-stamped return envelope and asking them to mail it back to the research team (if in-person contact is not possible) (see Appendices 6 and 7 for information letters and informed consent documents). Participants who are neither able to meet the researcher in person, or send the informed consent form by mail will be given the option of informed consent by telephone, which will be audio recorded using encrypted devices with audio files stored securely, similar to procedures in an existing study that tested a range of remote options for enrollment and consent of older people into research studies.[50] In case the participant is illiterate, the researcher will read the study information and consent form out loud to the participant. If they know how to sign, the participant will be asked to sign the informed consent form. If they are unable to sign the informed consent form themselves, a witness will be asked to sign to confirm that the information has been read out loud to the participant and that he/she understood and agreed to take part.

After having obtained informed consent from both the older person and the close family caregiver (if present), the researcher/research assistant will perform baseline measurements. In case the first contact with the participants occurred by phone, the researcher/research assistant will make an appointment to meet with them in the older person's home (or other preferred location). After obtaining baseline measurements, the researcher will check to which intervention arm the older person (and family caregiver) is randomised (see 2.2.1) using RedCap and inform them to which group they are assigned. In case the older person and close family caregiver (if

present) are randomised to the intervention group, the researcher/research assistant will inform them that they will be contacted by the navigator coordinator within one week. In case the patient and close family caregiver are randomised to the control group, the researcher/research assistant will tell them that they will be visited by the researcher after 12 weeks (approximately 3 months) and that they will be contacted by the navigator coordinator after 24 weeks (approximately 6 months). After each enrolment of a patient and family caregiver (if present), the researcher/research assistant will send the patient's contact details and group allocation to the navigator coordinator, who will then contact the patient and introduce the intervention at the appropriate time. As a visual aid, the researchers will give a leaflet to the participants with pictures of the different people involved in the study (i.e. researchers who will visit on a regular basis, intervention staff and names).

Data for primary, secondary, and tertiary or exploratory outcomes will be collected at baseline, at weeks 12, 24, 48 (and 72 in the control group) thereafter until the study end or until the patient's death (see figure under 2.1.6). For patients allocated to the intervention group, data collection will stop after 48 weeks; for those allocated to the control group, data collection will continue until 72 weeks after baseline. The researcher will try to perform the data collection with the patient (and their close family caregiver) within a timeframe of 1 week after each measurement time point.
Table 5 provides an overview of the measures used and information collected and the relevant time points for each throughout the study period. At each assessment point, the same measures will be administered, except for the collection of sociodemographic data that remain constant and that are collected at baseline only.

Data collection will be through structured questionnaires during a face-to-face contact with the patient/family (at his/her preferred place). Questionnaires for patients will be administered by a researcher in a structured interview, and answers will be filled in by the researcher on a paper version of the questionnaire. Questionnaires for close family caregivers will be self-administered on paper (in the presence of the researcher if support is needed). Given that the questionnaire for close family caregiver contains questions that may be perceived as sensitive by the participants (e.g. on informal care burden), questionnaires for close family caregivers will preferably be administered in the absence of the older person with cancer (e.g. in a separate room).

If data collection during a face-to-face contact is not possible (e.g. because of COVID or other reasons) we will allow remote data collection as contingency (but not preferred) option, either through administration of the questionnaire through an online form or in a structured interview format through video call (e.g. Zoom). The mode of data collection will be determined by the researcher prior to each measurement in consultation with the patient and family caregiver. In case of remote data collection, some people may require support of a family carer or friend, and the researchers will encourage such support. The project consortium has ample experience in both face-to-face and remote (including online) data collection with older people in poor health, especially during the COVID-19 pandemic when this was the only way to obtain research data from patients. These methods were found to be acceptable and feasible and to provide high-quality data, given careful preparation of the data collection including identifying which participants needed support for remote data collection and ensuring they have it.

Each assessment will last around 45 minutes for patients and 30 minutes for family caregivers, but this will be tested during feasibility testing of measurements prior to the trial. This was shown to be an acceptable procedure and duration in previous trials with a similar population.[51]

After participants complete the questionnaire/structured interview, the researcher will enter the de-identified responses into REDCap. REDCap is software for building and managing questionnaires and facilitating electronic data collection and storage. This database is accessed on a secure network server that is password protected.

Participants may withdraw from the data collection or voluntarily stop intervention sessions (e.g. because it is experienced as too burdensome, the patient is too busy, or too ill). The PI can also discontinue a participant from the study for the following reasons: due to an occurrence of an event, medical condition, or situation in which continued collection of study data would not be in the best interest of the client or the family caregiver. In case participants only wish to withdraw from the data collection, they may still continue with the intervention (visits by navigator) , if they wish so, and vice-versa. Reasons for discontinuing the data collection or intervention will be documented by the researcher/research assistant in REDCap, if participants wish to state them (they are not obliged to do so).

2.3.2 Data collection methods process evaluation

The process evaluation includes two phases: development phase (before intervention delivery) and evaluation phase (during and after intervention delivery). In the development phase, the original Canadian Nav-Care intervention (Nav-Care©) will be adapted to the European context, and further adapted to country and cultural-specific contexts by Local Adaptation Teams (LAT) of each country (see protocol in appendix 1). A report per country will be written, potential barriers and facilitators will be mapped, and the intervention will be pilot tested (see earlier). In the evaluation phase, the quality and quantity of the delivered intervention will be measured, and the role of context will be analysed, using CFIR[36] and RE-AIM[37], two well-established implementation science frameworks.

Short surveys for coordinators and navigators will be filled in shortly before the intervention starts, and at the end of the intervention period. During the intervention, the coordinators and trainers will keep diaries of their work, and navigators will fill in a short report of each client visit. After the intervention, each country will organize (group) interviews with navigators, coordinators, patients and family caregivers, and professionals involved in the recruitment and referral of patients. About 3-5 respondents per stakeholder group per participating setting in each country. The (group) interviews will be guided by topic lists based on CFIR and RE-AIM constructs.

For CFIR construct ‘innovation’, the Local Adaptation Team of each country will write a country report (development phase) and will fill in a short survey after the intervention (evaluation phase) (part of WP2, see protocol in appendix 1).
For CFIR construct ‘outer setting’ a researcher and trainer of each participating country will be interviewed by researchers of WP2, using a topic list (development phase and evaluation phase).

For CFIR construct 'inner setting' researchers of each country will interview the coordinator(s) and manager of each participating organization within their country, using a topic list (development phase and evaluation phase).
For CFIR construct 'characteristics of individuals' the coordinators, navigators and trainers of each participating country will fill in a short survey about confidence in taking their role (directly after their training and evaluation phase).
For CFIR construct 'Process' and 'RE-AIM dimensions (all evaluation phase):

- professionals involved in the recruitment and referral of patients will get a short survey every 2 months about referral and recruitment. (reach).
- trainers will keep a diary of all their activities, keep attendance lists of trainees (navigators and coordinators), and at the end of the trials an international group interview with trainers of each country will be held. (adoption)
- coordinators and trainers will keep diaries of their work, and navigators will fill in reports of each client visit during the intervention period. After the intervention, (group) interviews will be held with coordinators, navigators, patient/family carers. (implementation)
- coordinators, navigators, patients and family and professionals involved in the recruitment and referral of patients will be interviewed after the intervention. (implementation, maintenance)

Furthermore, information about RE-AIM dimensions will also come from data collection for the other CFIR constructs (see above).

Table 6 below provides a more detailed overview of what information will be collected, from which respondents, in which phase of the project. See appendix 8 for all data collection materials for the process evaluation and the informed consent documents.

Table 6 Overview measurements per group, measurement moment and what is measured

Target population	**Before intervention**	**During intervention**	**After intervention**	**CFIR/RE-AIM domains**
Local Adaptation Team	Country report about adaptation + short survey with specific questions about intervention characteristics		Short survey about evaluation intervention characteristics	CFIR: innovation, -,
Participating organizations (Manager + coordinator)	Interview about inner setting (barriers, facilitators)		Interview about evaluation inner setting and intervention (barriers and facilitators - greatest success, greatest barrier)	CFIR: inner setting
Coordinators	Short survey characteristics	Diary about process and recruitment	Short survey characteristics	CFIR: individual-characteristics

	individual		individual	
			(group) interview about experiences (barriers, facilitators, adaptations)	RE-AIM: reach implementation, maintenance
Navigators	Short survey characteristics Individual	Visit reports	Short survey characteristics individual	CFIR: individual-characteristics
			(group) interview about experiences (barriers, facilitators, adaptations)	RE-AIM: implementation, maintenance
Trainers	Diary about process / trainer after each training/mentoring session	Diary about process / trainer after each training/mentoring session	Group interview with all international trainers about experiences	RE-AIM: adoption, implementation maintenance
Professionals involved in the recruitment and referral of patients	Involved in LAT for feasibility check intervention	Short survey every 2 months about recruitment	Interview /short survey about evaluation intervention characteristics and recruitment/referral	CFIR: innovation RE-AIM: reach, maintenance
Patients/family		questions about experiences in WP3 survey	Interview about experiences	RE-AIM: implementation

2.3.3 Data management

The consortium certifies that all research activities will adhere most strictly to all applicable legal, ethical and safety provisions of the individual states and of the EU. Participants will conform to relevant EU legislation including (1) The Charter of Fundamental Rights of the EU, December 2009 and (2) EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (**GDPR**). All ethical issues of this project, the role of the **Ethics Evaluator** external to the project and the data management procedures are described below in section 3.

The Principal Investigator (Vrije Universiteit Brussel) will take the overall responsibility for data management over the course of the EU NAVIGATE project. Ultimately responsibilities for data management will be transferred to consortium partners to allow a collaborative and efficient collection of research findings throughout the time of the project.

A detailed Data Management Plan is provided in Appendix 9.

2.3.4 Analysis plans (outcome, subgroup, cost-effectiveness and process evaluation)

The Statistical Analysis Plan, the Subgroup and Country Comparative analysis plan, the Health Economic Analysis Plan, and the Process Evaluation Data Analysis Plan are extensively described in appendices 10, 11, 12, and 13 respectively.

2.4 Monitoring

2.4.1 Data monitoring

An Ethical and Data Monitoring Board is created to monitor the intervention and data collection and any adverse events (see next section) will be reported to them. This Boards consists of an **Ethics Evaluator,** and the **independent trial monitors**. The primary role of the Ethical and Data Monitoring Board will be to periodically review the accumulating data and determine if the trial should be modified or discontinued.

An Ethics Evaluator external to the project will be appointed who will monitor the ethical aspects of the study, including data management and privacy concerns. This person (or team) will provide evaluation and advice on ethical, legal, data protection and data management issues based on an audit of the reporting by the different national trial managers to the Overall Trial Manager and the independent trial monitors in the different countries. This evaluation will be done shortly after the start of the trial study, and at least at three follow-up occasions.

The monitoring evaluations will be conducted by national independent trial monitors.

The following files are intended to guide data monitoring:

- The **Investigator Site File** will be held at each participating site. It contains copies of relevant global study documents and all original site-specific documents.
- The **Trial Master File will** be held at the coordinating site (VUB). It contains all original global study documents and a copy of all site-specific documents of all participating sites.

Both the Investigator Site File and the Trial Master File will include all essential documents for the trial as described in the ICH E6 Guideline for Good Clinical Practice (section 8) such as Initiation Meeting, Training Log & Handover Documents, Delegation of Authority Log, CV's/GCP Certificates, Final Protocol/Amendments, Protocol/Amendment Signature Page(s), Notifications to and Approval Letter(s) from Regulatory Authorities, Progress Reports, Informed Consent Forms Version Log and Signature Page(s), etc.

2.4.2 Harms

Although older people with a life-threatening illness and their family caregivers are vulnerable groups, current evidence supports their participation in research that aims to understand and improve their well-being. The EU NAVIGATE study protocol, and the NavCare-EU intervention specifically, is non-invasive and does not pose any known risk of injury. It is a navigation intervention focused on identifying the needs of older people with cancer and their family caregivers and helping them access relevant resources to meet these needs. The intervention is not a formal psychotherapeutic intervention. Based on previous research and experience with the Canadian Nav-CARE intervention, adverse effects are unlikely. We define an adverse event as "*every event in the study that takes a course that is significantly more unfavorable to study participants than foreseen in the normal course of the illness"*. Any adverse events will be reported to the Ethical and Data Monitoring Board (see previous section). Adverse events are categorized as:

1) Anticipated or expected adverse events, which includes two categories (serious or not serious), and
2) Unanticipated or unexpected adverse events, which includes two categories (serious or not serious).

The only potential anticipated not serious adverse event is mild psychological discomfort or emotional distress to patients or family caregivers that may be caused by interactions with the navigator (e.g. in conversations about a patient's illness or prognosis) or through data collection (i.e. responding to questionnaires and interviews). Therefore, navigators will be trained and coached to deliver the Nav-CARE intervention and data collection will be conducted by researchers who are trained to work with this population. Moreover, participants will be informed that they can refuse to answer any question and may withdraw participation at any point in the study without negative consequence.

We will also put in place a series of procedures to identify and handle any signal of distress in patients, family caregivers and/or navigators.

1) The contact details of the respective researchers per country, the local ethics committee and the Data Protection Officer are mentioned on all information and consent letters and the questionnaires. Research participants will be encouraged to contact the researchers should they experience emotional distress related to study participation.
2) A written protocol for addressing queries and distress will be provided to all researchers, navigators, navigator coordinators, data collectors and trial managers. Any serious adverse events should be reported in writing to the Principal Investigator and lead researcher in the respective country (if not identical to PI) within 24 hours of occurrence or identification. Unanticipated (but non-serious) adverse events will be reported to the PI within two working days. If neither the PI or lead researcher is available, the trial manager in the respective country will be contacted. If an adverse event is reported, the PI fills out a form about the event and will forward that information to the appropriate ethics committee in their country following the mechanisms for reporting these events. The PI will provide a judgment as to whether the adverse event is associated with or related to the study protocol. The PI will also contact the Ethical and Data Monitoring Review Board to report the adverse event and consult them regarding the need to revise the protocol to prevent a recurrence of the adverse event.
3) If the adverse event concerns emotional distress that cannot be addressed by the researchers (e.g. through pausing data collection and reassuring the participant) they will direct the participant to appropriate help, e.g. the patients' general practitioner or other community-based services.
4) Researchers will keep a log record of their communications with study participants which will allow us to document instances of distress and how they were addressed and managed.

Since the study involves older people with cancer and in deteriorating health, some patients may die due to disease progression, or related to other illnesses, but this would not be related to the study protocol. Only in the very unlikely event if this would occur during or immediately before or after a data collection appointment, or during the participant's travel to or from the research appointment, their death will be reported to the data monitoring committee (see previous section).

A small risk of adverse events is related to trial conduct, specifically a risk for researchers conducting data collection from patients and family caregivers as this will often be done at patients' or family caregivers' homes. We will introduce a 'buddy system' and a pre-planned 'telephone chain', as is recommended for research on sensitive subjects such as life-limiting illness and palliative care.[47] One member of the research team, usually a senior collaborator or supervisor, will be nominated as point of contact (buddy) for each researcher who is collecting data. A second buddy will be nominated for when the first one is unavailable. The field researcher will contact the buddy just before the start of the data collection event (via a message or a phone call, but not via e-mail). The field researcher should then make contact with the buddy once again when the interview has ended (a 'return message'; again via message or phone call, not e-mail) and they are back in a place of safety (i.e. their home residence or their work office). The buddy should contact the field researcher after a pre-determined amount of time in case the latter did not communicate the end of data collection (e.g. after 2 hours for interviews) to ensure that the researcher has returned safely. Unanswered contacts should be followed-up with contact to the secondary buddy, the field researcher's regular or other colleagues, their next of kin, or, when these contacts are exhausted, the relevant authorities.

Given that data collection about sensitive topics can be burdensome for researchers, the team will organise regular – formal and informal – debriefing sessions.

2.4.3 Monitoring activities

The monitoring evaluations will be conducted by the independent trial monitors. The monitor should document and date all evaluations. In addition to the routine monitoring activities, the monitor will focus on the following trial specific items such as:

- Participants' eligibility: inclusion and exclusion criteria as per protocol
- Informed consent procedures
- Source data verification (a minimum of 20% of source data verification will be undertaken on parameters such is subject ID numbers, date of written consent, visit dates, etc.)
- Regulatory compliance: The monitor will ensure that any amendments have been correctly notified to the competent authority (CA) and that all necessary approvals are in place. The monitor will also evaluate that all annual reports have been completed and submitted in a timely manner to the correct regulatory bodies.
- Protocol compliance
- Safety monitoring: processing and reporting of adverse events (described below)
- Randomization processes to ensure that there is adequate documentation of the randomization
- Trial Master File/Investigator site file
- Data collection, storage, IT security
- Finance and contracts
- Monitoring reports: Monitoring Evaluation Reports will be produced by the monitor and sent to the overall Trial Manager. This report will be forwarded to the PI within 2 weeks after the evaluation.

Training before the start of the trial

For all researchers, data collectors and national trial managers in each country, online training sessions will be organized by the Overall trial manager, supported by the coordinators' researchers (VUB). The training will take place prior to the start of the pilot study (i.e. first participants' recruitment) in each country. The following points will be part of the training: protocol design, study-specific procedures, primary and secondary endpoints, safety reporting requirements, (e)CRF completion procedures, randomization procedures, patient compliance, and maintenance of trial master file/investigator site file. A description of the training will be provided in a Quality Assurance Manual. All research partners will receive a study initiation package before the start of the trial.

Interim monitoring activities during the trial
Auditing will be independent from investigators and the sponsor. The first Monitoring Evaluation in each country will take place approximately 6 weeks after the inclusion of the first participant in the pilot study, which allows that the first participants are recruited in the study and have experienced already some parts of the intervention to be monitored. Subsequent monitoring evaluations will be conducted during the trial. The interval for Monitoring evaluations will depend on recruitment rate, or quality issues.

3. Ethics and dissemination

3.1. Research ethics approval

This protocol is submitted for review and approval to the Medical Ethics Committees of all six participating EU NAVIGATE countries.
Each partner involved in data collection will obtain ethics approval from their local ethical committee before the start of the trial. The trial will be registered in a publicly accessible clinical trials registry www.clinicaltrialsregister.gov.

3.2. Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of participants or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require formal amendment to the protocol. Such amendment will be agreed upon by the EU Navigate consortium partners and approved by the Ethics Committee prior to implementation.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the EU Navigate consortium partners.

3.3. Consent or assent

After potentially eligible older people with cancer are identified from a range of settings where patients from the target population receive care, a researcher or research assistant will make an appointment with the potentially eligible participants to meet them in person (at the person's home or other preferred location) or will contact them by phone depending on their preference.

During the visit or phone call, the researcher/research assistant will explain the study, check eligibility criteria, and explore whether they are interested in participating. The researcher will also ask them whether there is a close family caregiver (someone who lives with them or is close enough to them to be present or provide informal care on a regular basis). If the older person with cancer has such a family caregiver, and s/he fulfils the inclusion/exclusion criteria, both will only be included into the study if both provide informed consent. Patients who do not have such a close family caregiver can also be included (see section 2.1.2.). Family caregivers of patients who do not agree to participant, cannot participate.
If all eligibility criteria are met, the researcher/research assistant will obtain informed consent from both the older person and the close family caregiver (if there is one).

Patients and family caregivers will be given the time they would like to consider participation and they will be assured that they are free to withdraw from participating in the study without any effect on their care. Participants will be made aware that consent is fluid and that they have the right to withdraw their consent at any time throughout the study without any negative impact on their healthcare or management. Written consent will be obtained without any coercion of study participants. The research team will provide all participants with the full disclosure about the nature and goal of the study. Participants will be given the opportunity to ask questions before they decide if they want to participate. After informed consent, the older person with cancer and their close family caregiver (if there is one) will then complete the baseline measurement. Only those who complete the baseline measurement are considered as enrolled in the study and will be randomized to the NavCare-EU intervention or control group (delayed start of intervention). If participants decide to withdraw from the study, they will still receive all available standard care.

3.4. Confidentiality

All project partners will take all required steps to guarantee compliance with the provisions of the EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR) as well as the related legislation of the Member States of the project partners.

The study will be carried out respecting the principles of the Charter of Fundamental Rights of the European Union. These include dignity, freedom, equality, solidarity, citizens' rights and justice. The study also complies with Article 7 and 8 of the European Human Rights Convention. In particular, researchers will consider the sensitive implications of their agendas for privacy and autonomy.

Data security
The study will follow the International Standard ISO/IEC 17799 covering data security under the topic of information security. One of its main principles is that all stored information, i.e. data, should be "owned", so that it is clear whose responsibility it is to protect and control access to that data, to keep it safe from corruption and involuntary disclosure outside the European Economic Area. The coordinating partner (VUB) will monitor compliance with data security measures in consultation with the institutional Information Security Officer and the institutional Data Protection Officer (dpo@vub.be). The Data Management Plan is added as Appendix 9.

Data protection

The data will be collected via REDCap, a secure web application, in alignment with GDPR. The data will be stored on the secure server of the UZ Brussels. Data access is strictly limited to those who require access to perform the research. Only pseudonymized data will be accessible for all the researchers. The security on this server is frequently updated. A security consultant of the UZ Brussels is available to handle any problems that might arise. The server has a back-up power supply and cooling system to avoid mechanical failure leading to data loss. The server is physically secure and kept in a locked room with CCTV. Each participating researcher at each university will receive a log-in code and be able to download the data to their own storage device via an encrypted (sftp) connection. Data will only be stored on encrypted password-protected devices.

The recording of the qualitative interviews will be transcribed verbatim. Upon doing so, all personal data will be removed, and names will be replaced by aliases. Interview transcripts will receive a code. The key to the code will be kept in such a way that identification of the participants is only possible for authorized researchers. The mapping table which enables the identification will be stored in a separate folder, only accessible by these authorized researchers. After the transcriptions the audio recordings will be uploaded unto a secure external server, only accessible by the researcher of the EU NAVIGATE consortium. The original recordings on the recording device will be deleted.

Written informed consent of the participants will be sought containing a detailed and written explanation of data security, ownership, and the rights of the data subjects. A record of the processing activities will be kept. The signed informed consents will be stored in a closed room at each of the participating institutions in the 6 countries, which is only accessible by the researchers involved in this project.

Data sharing

Information sharing between partners of the EU NAVIGATE consortium: All participants in NavCare EU intervention will sign an informed consent, clarifying all implications in terms of privacy and protection of their personal data. Pseudonymized data will be shared between the consortium partners of the EU NAVIGATE project via the secure external server. This server will be password protected and only researchers involved in the study will have access to the data. Each participating researcher at each university will receive a log-in code and be able to download the data to their own storage device via an encrypted (sftp) connection. Data will only be stored on password-protected devices.

Personal data sharing: Data will be pseudonymized and only shared to third parties after signing a unilateral data sharing agreement, only after evaluation by the DPO if compatible grounds for scientific research apply. Approval of an ethical committee for the research will also be necessary.

3.5. Declaration of interests

There are no financial and other competing interests for principal investigators for the overall trial and each study site.

3.6. Access to data

Anybody interested in replicating the research findings or the intervention, disseminating them to a wider audience, or translating the outcomes of the project into policy can make use of our data. This will increase the relevance and visibility to the public of EU NAVIGATE. But because the files will contain confidential information and/or direct and indirect identifiers (sensitive new data collected during the project) it will only be shared with third parties upon reasonable request and upon signing a unilateral data sharing agreement as these data fall under GDPR (restricted access). The signing of a unilateral data sharing agreement will prevent the further dissemination of sensitive data. Other data and outputs such as the NavCare-EU intervention toolkit, guidelines and reports will be made publicly available under a Creative Commons licence and will be published online on the project website at the end of the project (2027) and on the online secure repository Zenodo. These data will be given the best chances for being maximally used.

3.7. Ancillary and post-trial care

Participants in the trial are referred to specific existing services or community resources based on the problems or needs identified during the intervention visits with the navigator (ancillary care) or after the trial (post-trial care).During the study, all participating patients (of both the intervention and the control group) will receive the NaveCare-EU intervention for a period of one year. After the trial, implementation organisations that were involved in the trial can decide that their volunteers may continue supporting the patients as part of their normal practice. Hence, the volunteers and the support relationship established may continue if both the patient and the volunteer want this. If the study shows that the intervention works, elements of the NavCare-EU intervention may be adopted in the normal practice of the implementation organisations, depending on available resources.

3.8. Dissemination policy

To achieve the expected outcomes and impacts of EU Navigate, we will use an extensive dissemination and exploitation strategy and apply a broad range of communication activities about the results and their implications. Resources for a distinct dissemination, exploitation and communication strategy are allocated from the start of the project and a Work Package for this strategy (WP8) will ensure the adequate management of the strategy.

The EU NAVIGATE consortium is built up carefully to reach different target groups and to maximize societal, scientific and economic impact of the project both within and beyond the participating countries. The three dissemination partners E.C.O., AGE and EAPC are influential European umbrella organizations that together connect with a diverse network of member organizations and other stakeholders, covering the domains of cancer care (E.C.O.), ageing (AGE), and palliative care (EAPC), and reaching different target groups at regional, national, European, and international level. Additionally, an **International Advisory Board (IAB)** has been set up for the project, composed of European organizations representing older people and patients, family caregivers, and health care providers of different disciplines in Europe. They will be consulted on a yearly basis concerning the project's aims, results and impacts. Together, these

organizations have active networks tapping into the most important target groups of EU NAVIGATE, facilitating the uptake, diffusion, deployment, and use of project results and outcomes by the target groups.

Six specific dissemination objectives (DOs) are defined to inform the scientific community about the project results. Publishing is aimed in open access, green and gold international journals but also in national topic specific journals. In addition, oral and poster contributions to international conferences related to the fields covered by EU NAVIGATE will be realized.

1. **Disseminate through PhD dissertations.** At least 6 PhD dissertations will be completed within the EU NAVIGATE project. Impact will be measured as such.
2. **Disseminate through publication in international journals.** We will publish the results in international high-impact factor open access journals with peer-review. Impact measurement: All the full-time junior researchers hired on the project will be expected to complete at least 2-3 articles for peer-reviewed journals, in addition to articles written by senior and postdoctoral researchers involved in the project. This means that at least 15 articles can be expected to come out of the EU NAVIGATE project, concerning various aspects of the project.
3. **Disseminate through publication in national journals.** The project results will be published in several contributions in national journals oriented towards healthcare providers. Minimum target: 7.
4. **Disseminate to and interact with all scientific stakeholders through active contributions at international conferences.** The project partners aim at disseminating project results at relevant scientific conferences in the field of palliative care, oncology and supportive care in cancer, geriatrics, and public health.
   The actual impact will be measured by the number of conference contributions. Minimum target: 25.
5. **Disseminate to and interact with all scientific stakeholders through joint activities with other EU-funded projects.** Consortium partners will organize and participate in networking and joint activities with other EU-funded projects to facilitate the exchange of knowledge and best practices along projects. Networking events for researchers of EU NAVIGATE, DIAdIC (H2020), MyPal (H2020) and iLIVE (H2020) organized by the EAPC.
6. **Disseminate to and interact with all scientific stakeholders through own organized events**: The consortium plans to organize 4 workshops dedicated to the project. Impact will be measured by the number of participants.

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Appendices

- Appendix 1. Protocol for translating, adapting, and piloting (stage 1&2) the intervention in each country.
- Appendix 2. Pilot study. Fictional cases and reporting template
- **Appendix 4.** Pragmatic trial. **Interview older person with cancer**
- **Appendix 5.** Pragmatic trial. **Questionnaire close family caregiver**
- Appendix 6. Pragmatic trial. Information letter and informed consent document older person with cancer.
- Appendix 7. Pragmatic trial. Information letter and informed consent document close family caregiver
- Appendix 8. Pragmatic trial. Measures for process evaluation and informed consent documents
- Appendix 9. **Data management plan**
- Appendix 10. **Statistical analysis plan**
- Appendix 11. **Subgroup and Country Comparative Analysis plan**
- Appendix 12. **Health Economic Analysis plan**
- Appendix 13. **Process Evaluation Data Analysis plan**
- Appendix 14. **NavCare EU Intervention toolkit**

Administrative information

TRIAL FULL TITLE	An international pragmatic randomised controlled trial to evaluate the NAVCare-EU intervention for older people with cancer and their family caregivers
SAP VERSION	V3.0
SAP VERSION DATE	26/10/2023
PROTOCOL VERSION	V1.0
PROTOCOL VERSION DATE	07/04/2023
EUDRACT NUMBER	To follow
CLINICALTRIALS.GOV IDENTIFIER	To follow
SPONSOR	Funded by the European Union (GA number: 101057361)
TRIAL CHIEF INVESTIGATOR	Prof. Van den Block Lieve, End-of-life Care Research Group, Vrije Universiteit Brussel (VUB) and Ghent University
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The first version of the SAP was written before recruitment start, to submit to the ethics committees (EC). It should be read alongside the protocol.

SAP revision history

SAP version no.	Date	Author	Justifications for each SAP revision	Timing of SAP revision in relation to interim / final analysis
1.0	12/04/2023	SDB	/	Prior to analysis, prior to data lock, prior to start enrolment, prior to submission to the EC
2.0	20/04/2023	SDB	Minor corrections following review by project team	Prior to analysis, prior to data lock, prior to start enrolment, prior to submission to the EC
3.0	26/10/2023	LP	Minor corrections following review by project team	Prior to analysis, prior to data lock, prior to start enrolment

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Signature page

Dr. De Buyser Stefanie (SAP author + senior statistician) Stefanie De Buyser Digitally signed by Stefanie De Buyser Date: 2023.10.26 16:24:10 +02'00'
Prof. Van den Block Lieve (chief investigator) 
Dr. Miranda Rose (SAP reviewer) 
Prof. Pivodic Lara (SAP reviewer) 
Prof. Smets Tinne (SAP reviewer) 

Abbreviations

CI	Confidence interval
EC	Ethics Committee
EORTC	European Organisation for Research and Treatment of Cancer
LMM	Linear Mixed model
MAR	Missing At Random
MNAR	Missing Not At Random
REDCap	Research Electronic Data Capture
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
QL	Quality of Life

Introduction

Background and rationale

Contemporary cancer care for older populations needs an innovative, effective, and cost-effective concept or approach to sustainably meet the increasing demand for high-quality, supportive, palliative, and end-of-life care within existing EU healthcare systems.

Navigation interventions or programs hold promise to meet these needs. Scientific evidence for patient and family navigation mainly comes from the US and Canada and suggests favourable feasibility and effectiveness, and promising results of cost-effectiveness for patient navigation in cancer care, specifically during the beginning phases of illness, i.e. cancer screening and diagnosis, and more recently in improving cancer treatment and care (Bernardo et al, 2019; Roland et al, 2017). Evidence for its use in supportive, palliative, end-of-life care is much weaker (72% of studies of navigation program in cancer focused on the early phases) and particularly in older cancer populations (Bernardo et al, 2017; van Ee et al, 2017).

The Canadian Nav-Care© programme is a person- and family-centered navigation intervention. It has potential to improve quality of life and wellbeing for older cancer patients and their family caregivers. Nevertheless, high-quality research designs such as pragmatic randomized controlled trials or studies using a control group have not been used to evaluate Nav-Care. In addition, it needs yet to be adapted and evaluated in European health care systems, using high-quality research designs and measurements.

Objectives

The primary objectives are to evaluate the effectiveness of the NavCare-EU intervention compared with care as usual for improving global health status / quality of life and level of social support in older persons with cancer living at home.

A secondary objective is to evaluate the effectiveness of the NavCare-EU intervention compared with care as usual for reducing caregiver burden in close family caregivers of older persons with cancer living at home.

Exploratory objectives are to explore the uniformity of the intervention effect compared with care as usual across

- different subgroups defined by baseline characteristics known to affect health equity and equitable access
- different health care systems and care regimens in Europe.

Endpoints

Primary endpoints

- Change from baseline at 24 weeks in global health status/quality of life as measured by the 2-item subscale from the EORTC QLQ-C30 (version 3.0) in older persons with cancer
- Change from baseline at 24 weeks in levels of social support (i.e. emotional/informational support, tangible/instrumental support, positive social interaction, and affection) as measured by the Medical Outcomes Study Social Support Survey in older persons with cancer

Secondary endpoints

- Change from baseline at 24 weeks in feelings of loneliness as measured by the 3-item-UCLA Revised Loneliness Scale in older persons with cancer
- Change from baseline at 24 weeks in Caregiver burden as measured by the Zarit Burden Interview Short Form in close family caregivers of older persons with cancer

Exploratory endpoints

Change from baseline at 24 weeks in:

- Symptoms or problems experienced (i.e. as measured by the symptom scales/items and the emotional functioning scale from the EORTC QLQ-C30 (v 3.0) in older persons with cancer
- Well-being of older people as measured by the Well-Being of Older People measure (WOOP), which captures a comprehensive set of well-being domains relevant to older people (broader than health)
- Knowledge of resources and services and confidence in decision-making, as measured by the Items from Patient Engagement Survey Canada in older persons with cancer
- Health status as measured by the EQ-5D in older persons with cancer and for family caregivers
- Health and social care services and resource use as measured by the Adapted Client Services Receipt Inventory in older persons with cancer
- Positive Aspects of Caregiving as measured by the Positive Aspects of Caregiving (PAC) questionnaire in family caregivers of older persons with cancer

Change from baseline at 48 weeks in the primary and secondary response variables.

- Time since randomization until death, in days, with censoring at 48 weeks after randomization

Study Methods

Trial design

- Multicentre (6 EU countries with 1 implementation site per country, except for Belgium (2 implementation sites) and the Netherlands (3 implementation sites)
- Pragmatic fast-track randomized controlled trial
- Superiority
- Parallel-group
- 1:1.08 allocation ratio (Control:Intervention) in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal
- 1:1.45 allocation ratio (Control:Intervention) in Poland
- Non-blinded
- Partially nested design until week 24: patients in the intervention group are clustered within navigators, but patients in the control group are not (for the analysis of primary outcomes)
- Fully nested design from week 24 onwards

Interventions

Intervention = the NavCare-EU intervention plus care as usual

Patients allocated to the intervention group will immediately receive the NavCare-EU intervention plus care as usual for 48 weeks (12 months). The NavCare-EU intervention is a face-to-face and tele-

supported non-pharmacological intervention. The central component is a patient navigator, a dedicated person with or without a health-related background who engages with patients on an individual basis.

Navigators collaborate with patients and family caregivers throughout the continuum of supportive, palliative, and end-of-life care. Their main activities focus on addressing the needs, quality of life, and wellbeing of patients and family caregivers, the provision of information and psychosocial support, and ensuring people can connect to and access necessary services or resources. Every two weeks, navigators have face-to-face and/or telephone or IT-supported contact with patients and family carers, or in different intervals, as needed.

In the case of volunteers as navigator, expected caseload is one or two patients per navigator; in the case of professionals, a higher caseload per navigator is possible. The mean number of patients per navigator is expected to be 1.5 in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal, and 10 patients in Poland.

Navigators are matched to patients and family carers by navigator coordinators. Navigators and coordinators are trained, coached, and mentored by a navigation trainer.

International trainers will aid country trainers to implement the intervention in their specific healthcare contexts and address country-generic and country-specific barriers and facilitators.

Control = care as usual

Patients allocated to the control group will first receive care as usual for six months (24 weeks) followed by the NavCare-EU intervention plus care as usual for 12 months (48 weeks).

A description of usual care for each country will be provided prior to trial start.

Randomization

- Randomization will take place after all baseline measurements have been completed.
- We will randomized patients in a 1:1.08 allocation ratio (Control:Intervention in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal and in a 1:1.45 allocation ratio (Control:Intervention) in Poland. These are the most efficient allocation ratio's given the partially nested design (see sample size calculation).
- We will use permuted block randomisation with varying block sizes.
- Randomisation will be stratified by country.
- Randomisation lists will be uploaded in REDCap (Research Electronic Data Capture). REDCap is a secure web-based software platform designed to support randomisation and data capture for research studies.

Sample size

To achieve at least 80% power to detect a mean difference between groups of 10 points in patient's global health status/quality of life using an analysis of covariance (ANCOVA) adjusted for baseline global health status/quality of life, at the two-sided 2.5% significance level assuming a standard deviation of 25 points and a correlation of 0.3 between baseline and 24 weeks, a total sample size of 220 patients is needed with a balanced design (allocation ratio 1:1).

Taking into account the partially nested study design (there is only a cluster effect of navigators in the intervention group), 115 patients in the control group and 131 patients in the intervention group is most efficient, assuming on average 1.5 patients per navigator in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal (recruiting about 5/6 of all patients), and 10 patients per navigator in

Poland (recruiting about 1/6 of all patients), and an intra-cluster correlation (ICC) of 0.10. Anticipating a drop-out rate equal to 50% (17.5% due to mortality, 32.5% due to other reasons), 229 subjects in the control group and 260 subjects in the intervention group are needed (total sample of 489, of which 81 patients from Poland and 83 patients from the other countries).

The sample size calculation was performed using SAS software (version 9.4) and is based on the paper from Moerbeek and Wong (2008).

The sample size calculation is based on the following assumptions:

1) A mean difference between groups of 10 points is considered the smallest clinically relevant difference in the mean score of EORTC QLQ-C30 (EORTC Quality of Life Group, 2008).

2) The standard deviation of 25 points reflects the heterogeneity in the score at 6 months in EORTC QLQ-C30 in a similar usual care population (EORTC Quality of Life Group, 2008).

3) An ICC of 0.1 was chosen as a conservative estimate as there is currently no empirical data to support an exact estimate of the ICC.

4) A correlation between baseline and 24 weeks in baseline global health status/quality of life of 0.3 was chosen as a conservative estimate considering that correlations for longitudinal measures are very rarely below 0.5.

5) A drop-out of 50% is a more conservative estimate than those reported in the Nav-Care feasibility and pilot studies (35% over 1 year, 40% over 1 year, 17% over 6 months) (Duggleby et al, 2021; Pesut et al, 2020; Pesut et al, 2017). Moreover, the final analysis will include the available information from patients who drop out.

6) A significance level of 2.5% was chosen to control the Type I error rate, because the trial is designed so that two study endpoints could lead to a conclusion that effectiveness is established (Bonferroni correction).

We estimate an enrolment rate (patients enrolled out of all deemed eligible) of 55%. This includes an estimated 10% not being eligible because the family caregiver does not agree to participate, based on a palliative care pilot RCT in older people conducted by P1 VUB (de Nooijer et al 2021). **This means we estimate to approach 151 patients per country in Belgium (Flanders), Ireland, Italy, the Netherlands, and Portugal to enrol 83 and 148 patients in Poland to enrol 81.**

Framework

For all endpoints, the null hypothesis will be that there is no true difference between the NavCare-EU intervention and care as usual (superiority).

Statistical interim analyses and stopping guidance

No interim analyses to stop for efficacy or futility are planned.

Timing of final analysis

Analysis will take place in separate stages. First, the primary endpoints at week 24 will be analyzed. The subgroup analyses and the additional exploratory analyses (see further) will be performed at a later stage.

Figure 1 illustrates the timing of the schedules of enrolment, interventions, assessments, and participant visits. Data analyses will commence at least 6 months after completion of data collection per follow-up point, and we will aim to submit findings for publication within one year of starting data analysis.

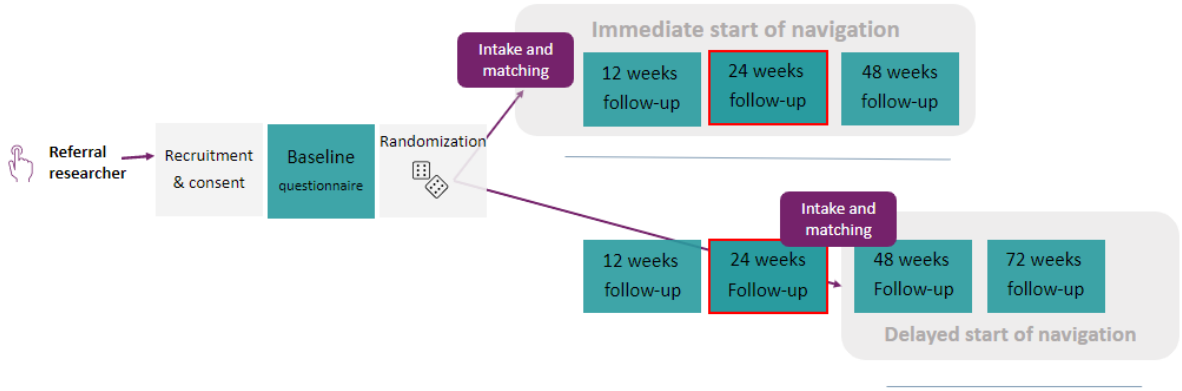

Figure 1. Time schedule of enrolment, interventions, and assessments

Timing of outcome assessments

For the intervention group, outcomes will be measured at baseline (T0), 12 weeks (T1), 24 weeks (T2) and 48 weeks (T3) (see Figure 1). For the control group, outcomes will be measured at baseline (T0), 12 weeks (T1), 24 weeks (T2), 48 weeks (T3) and 72 weeks (T4).

Statistical Principles

Confidence intervals and P values

All hypothesis testing will be two-sided. The two primary endpoints will be tested at the 2.5% significance level (Bonferroni correction for multiplicity). The confidence intervals (CIs) for the estimated mean differences in the primary endpoints will be 97.5% CIs.

No adjustment for multiplicity will be made for other endpoints, as the results on these endpoints will only be interpreted after superiority on at least one of the primary endpoints can be demonstrated. Comparisons of secondary endpoints will be performed at the 5% significance level. Comparisons of exploratory endpoints and subgroup analyses should be considered as hypotheses-generating (not conclusive) and interpreted with care.

All reported CIs (other than the ones for the estimated mean differences in the primary endpoints) will be 95% CIs.

Interpretation

The NavCare-EU intervention will be considered as beneficial if statistically significant and clinically relevant improvement compared with care as usual can be demonstrated on at least 1 of the 2 primary endpoints. Hence, NavCare-EU will be considered effective if the estimated effect on at least one of the endpoints is considered statistically significant ($p < 0.025$) and clinically relevant (≥10 points difference).

Analysis populations

All analysis will be performed on the intent-to-treat (ITT) population, which consists of all patients randomized. Subjects are analyzed according to the allocated intervention group irrespective of their compliance with the planned course of intervention. The ITT approach may reflect the effects of NavCare-EU on the different endpoints in daily practice.

Trial Population

Screening data

The total number of persons with cancer who are assessed for eligibility will be reported, together with reasons for not being willing to participate.

Eligibility

The inclusion and exclusion criteria are specified in the protocol. The number of ineligible persons with cancer randomized and the number of ineligible family caregivers included will be reported, together with reasons for ineligibility.

Recruitment

A CONSORT flow diagram will be used to summarize the number of persons with cancer who:

- gave informed consent
- were randomized
- received the allocated intervention
- did not receive the allocated intervention*
- lost to follow-up*
- discontinued the intervention*
- included in the primary analysis
- excluded from the primary analysis*

*reasons will be provided (e.g. withdrawal, death, etc).

Withdrawal / Follow-up

Participants may withdraw from the intervention or from data collection. The PI can also discontinue a participant from the intervention in case of (1) significant study intervention non-adherence, (2) loss to follow-up, or (3) occurrence of an event, medical condition, or situation such that continued intervention would not be in the best interest of the participant. Reasons for discontinuing the intervention or data collection will be documented by the researcher/research assistant. In case participants only wish to withdraw from the intervention, they are invited to continue with data

collection, and priority will be given to collection of primary outcomes. Data collected after day of study withdrawal will not be used for analysis.

The numbers (with reasons) of withdrawals over the course of the trial will be summarized by treatment arm.

Baseline characteristics

Patient characteristics

- **socio-demographic characteristics** - age, gender, country of birth, the country(ies) where the mother and father were born, highest educational level completed, whether the patient identifies with a specific religion or belief, with whom the patient currently lives, marital/partnership status, number of people that the patient consider to be important for them over the last 12 months and the extent to which the patient feels they can make ends meet (financial status).
- **clinical characteristics** - organ or part of the body where the cancer was located and where it started, whether the cancer metastasized, age at diagnosis, comorbidities
- **functional status** – Clinical Frailty Scale

Close family caregivers

- **socio-demographic characteristics** – age (years), gender, country of birth, country(ies) where the mother and father were born, highest educational level completed, whether the family caregiver identifies with a specific religion or belief, , relation to the patient, whether they live together with the patient, average number of hours spent with the patient during the last week, average number of hours a week used to provide direct care to the patient, and current employment status.

Using descriptive statistics, the characteristics of patients and their close family caregivers at baseline will be described and summarized, both for the control group and the intervention group. Continuous data will be summarised using mean and standard deviation (SD) if normally distributed, and median and 25^{th}, 75^{th} percentiles if not normally distributed. Categorical variables will be described using frequencies and percentages.

Analysis

Outcome definitions and derivations

We will use established and validated measures for all outcomes. Each outcome measure is a summary score of multiple items. Scores for global health / quality of life are computed if at least 50% of the items are valid (EORTC Quality of Life Group, 2001). Other summary scores are computed if at least 70% of the items are valid. In case of missing items, summary scores are the weighted sum of the observed items with weights inversely proportional to the number of valid items.

Analysis methods

All endpoints are continuous variables. We expect them to have a (log)normal distribution. Hence, linear mixed models (LMMs) for a normal distribution with identity link will be fitted. The random

effects part of the models will contain a random intercept for navigator and a random intercept for participant ID (patient ID / caregiver ID) nested within navigator for endpoints assessed in older persons with cancer / family caregivers respectively. The fixed effects part of the models will include group (intervention vs usual care), time point (post-intervention measurement at 24 weeks vs. baseline), their interaction group x time, and country (stratification factor for randomization). The interaction effect will capture the mean difference between groups in change from baseline. Estimated marginal means with corresponding CI will be reported.

Covariates

The FDA recommends adjusting for baseline covariates that are anticipated to be most strongly associated with the outcome of interest. Adjustment for these baseline covariates will generally reduce the variability of estimation of treatment effects and thus lead to narrower confidence intervals and more powerful hypothesis testing.

Because randomization is stratified by country, the models are adjusted for country. Otherwise, the standard error is likely to be overestimated and interval estimation and hypothesis testing can become unduly conservative.

For the analysis of the primary endpoint social support, as measured with the Medical Outcomes Study Social Support Survey (MOS), the model will include as covariate the older person's living situation, dichotomized as living alone vs not living alone.

No covariates are included in the analyses of the other primary endpoint.

Subgroup analyses

Subgroup analyses (led by the partner at University of Coimbra) will be performed (to explore the uniformity of the intervention effect compared with care as usual across on the primary and secondary endpoints. More information about the subgroup analyses and country comparative analysis plan will provided at a later time.

Missing data

Missing baseline characteristics

Missing values in the descriptive analysis of the baseline characteristics will be reported as missing. Missing baseline covariate data is assumed to be missing completely at random.

Missing outcome data

The LMM is fitted based on restricted maximum likelihood (REML). The analysis includes the available information from subjects with missing outcome values and yields valid inferences under the assumption that missing outcome data are missing at random (MAR). In our main analyses, we assume that missing outcome data can be related to the allocated intervention, baseline value of the outcome, and/or country, but that it is unrelated to other values. We will perform sensitivity analyses regarding the assumption behind the missing outcome data generating mechanism.

Sensitivity analyses

We will perform several sensitivity analyses for the primary endpoints, all regarding the assumption behind the missing data generating mechanism. In a first sensitivity analysis, we will make the MAR

assumption more plausible by including extra covariates (age category, functional status) in the fixed effects part of the LMM.

Given the expected dropout due to death, the MAR assumption might be too restrictive, therefore sensitivity analyses will be performed allowing a missing not at random (MNAR) mechanism. More specifically, starting from the MAR model, a jump-to-reference and tipping-point analysis will be applied. Additionally, another sensitivity analysis will be performed to deal with missingness due to death. We will estimate the effect of intervention among the unobservable subpopulation that would have survived under either arm (Chiba and VanderWeele, 2010). This is a conservative estimate of the intervention effect of interest.

Additional exploratory analyses

The control group will receive care as usual for six months (24 weeks), followed by the NavCare-EU intervention for 12 months (48 weeks). In this group, outcomes will also be assessed at 72 weeks from randomization, which corresponds to 48 weeks from the start of the intervention.

Time since start of the intervention	Time since randomization	
	Intervention group	Control group
0 weeks	0 weeks	24 weeks
24 weeks	24 weeks	48 weeks
48 weeks	48 weeks	72 weeks

We will assess if receiving the NavCare-EU intervention 24 weeks after randomization is non-inferior to receiving the NavCare-EU intervention immediately after randomization, with respect to mean **change from start of the intervention** at 48 weeks in the primary and secondary endpoints. Similar LMMs as described for the main analyses will be fitted, but timepoints (week 48) will relate to the start of the intervention instead and not to randomization. A difference between groups less than 10 is considered not clinically relevant (non-inferiority margin).

Another additional exploratory objective is to assess mean differences over time in the primary and secondary endpoints. We will compare the estimated marginal mean responses (averaged over allocation groups) between timepoints (where timepoints relate to the start of the intervention and not to randomization).

Statistical software

Analyses will be conducted in R version 4.2.2 or more recent. The primary analyses will be repeated using SAS software (version 9.4 or more recent).

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ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: October 25, 2023

ClinicalTrials.gov ID: [Not yet assigned]

Study Identification

Unique Protocol ID:	1432023000143
Brief Title:	International Study to Evaluate a Navigation Program for Older People With Cancer and Their Family Caregivers (EU NAVIGATE Study).
Official Title:	Study Protocol for an International Pragmatic Randomised Controlled Trial of the NavCare-EU Intervention for Older People With Cancer and Their Family Caregivers.
Secondary IDs:	101057361 [Grantor or Funder: Horizon Europe]

Study Status

Record Verification:	October 2023
Overall Status:	Not yet recruiting
Study Start:	November 15, 2023 [Anticipated]
Primary Completion:	May 2025 [Anticipated]
Study Completion:	May 2026 [Anticipated]

Sponsor/Collaborators

Sponsor:	Vrije Universiteit Brussel
Responsible Party:	Principal Investigator Investigator: Lieve Van den Block [lvandenblock] Official Title: Professor of ageing and palliative care Affiliation: Vrije Universiteit Brussel
Collaborators:	University of Dublin, Trinity College Uniwersytet Jagiellonski Amsterdam UMC, location VUmc University of Coimbra University Ghent University of British Columbia Lega Italiana per la Lotta contro i Tumori

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved

Approval Number: EC-2023-164
Board Name: Commissie Medische Ethiek Reflectiegroep Biomedische Ethiek
Board Affiliation: Universitair Ziekenhuis Brussel
Phone:
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Data Monitoring: Yes

FDA Regulated Intervention: No

Study Description

Brief Summary: Most people with cancer are older, and this affects millions of Europeans yearly. Integrating high-quality, equitable, and cost-effective care across the continuum of supportive, palliative, and end-of-life care for both patients and family caregivers is highly relevant from a healthcare, prevention, and economic perspective.

EU NAVIGATE is an interdisciplinary, cross-country, and intersectoral project funded by the European Union. The overall aim of the study is to evaluate the effectiveness and cost-effectiveness of a patient and family navigation intervention (NavCare-EU) for older people with cancer and declining health and their family caregivers in different healthcare systems in Europe. Nav-Care EU is a person- and family-centered non-pharmacological intervention in which navigators collaborate with patients and families to improve quality of life and improve levels of social support, foster empowerment, and facilitate timely and equitable access to health and social care services and resources as needed, throughout the supportive and palliative care continuum. NavCare-EU is based on the existing and successfully tested Nav-CARE(c) intervention from Canada.

Effectiveness and cost-effectiveness will be evaluated through an international 6-country multisite pragmatic fast-track randomised controlled trial (RCT) with an embedded mixed methods process evaluation to compare the NavCare-EU intervention in addition to standard care with the provision of standard care alone. The RCT and process evaluation will be conducted in Belgium (Flanders), Ireland, Italy, the Netherlands, Poland, and Portugal. Participants are people with cancer and declining health, who are aged 70 years and older, as well as their close family caregivers.

Specific objectives are:

1. To compare the NavCare-EU intervention to care as usual, in terms of its:

    1. Effectiveness on (1) global health status/quality of life, and the levels of social support (two co-primary outcomes); and on feelings of loneliness of older persons with cancer across the continuum of supportive, palliative, and end-of-life care; (2) family caregiver burden
    2. cost-effectiveness
    3. effects on different subgroups defined by characteristics known to affect health equity and equitable access, i.e., gender, age, socioeconomic status, extent of social support and living situation, and geographical location (rural vs. urban)
    4. effectiveness and cost-effectiveness in different health care systems and care regimes in Europe

2. To evaluate the implementation processes of the NavCare-EU intervention and the feasibility of its integration in different health care systems and care regimens in Europe, the contextual barriers and facilitators for effective and

	sustainable implementation, and the mechanisms involved in reaching the outcomes in each country, as perceived by patients, family caregivers, and other care providers
Detailed Description:	

Conditions

Conditions:	Cancer (Active Cancer, Meaning Not Being Cancer Free), of Any Stage and Involving Any Treatment/Care Regimen; i.e. Curative, Life-extending, or Palliative
Keywords:	palliative care supportive care cancer family caregiver older people community primary care

Study Design

Study Type:	Interventional
Primary Purpose:	Supportive Care
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	489 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: intervention group In EU NAVIGATE, participants in the intervention group will receive a navigation intervention (also called NavCare-EU), alongside any usual care. Navcare-EU is a person- and family-centered navigation intervention, aimed at supporting older people with cancer throughout the care and illness continuum, via the involvement of a patient/family navigator. Navigators focus on connecting clients to social supports, both formal and informal, advocating for clients in meeting their quality-of-life goals, resourcing by identifying needs and negotiating access to meeting those needs, and engaging clients in what is most meaningful to them. Navigators are selected, trained, and mentored volunteers or professionals. NavCare-EU is based on the existing and successfully tested Nav-CARE(c) intervention from Canada.	Behavioral: NavCare-EU NavCare-EU is a person- and family-centered intervention in which navigators collaborate with older persons and their close family caregivers across the continuum of supportive, palliative, and end-of-life care,. NavCare-EU is based on the existing and successfully tested Nav-CARE intervention from Canada. Navigators focus on connecting clients to social supports, both formal and informal, advocating for clients in meeting their quality-of-life goals, resourcing by identifying needs and negotiating access to meeting those needs, and engaging clients in what is most meaningful to them. Navigators are selected, trained, and mentored volunteers or professionals. NavCare-EU is based on the existing and successfully tested Nav-CARE(c) intervention from Canada.
No Intervention: control group Participants in the control group will receive what is usual care in each of the participating countries for 24	

Arms	Assigned Interventions
weeks (primary trial outcome). After 24 weeks, they will also receive the navigation intervention (NavCare-EU) (fast-track RCT).	

Outcome Measures

Primary Outcome Measure:

1. Global health status/quality of life of the older person with cancer
   Global health status/quality of life of the older person with cancer, measured with 2-item subscale from the EORTC-QLQ-C30 (revised) measuring health-related quality of life.

   [Time Frame: Change from baseline at 24 weeks.]

2. Levels of social support of the older person with cancer
   Levels of social support of the older person with cancer measured with the Medical Outcomes Study Social Support Survey (MOS)

   [Time Frame: Change from baseline at 24 weeks.]

Secondary Outcome Measure:

3. Feelings of loneliness of the older person with cancer
   Feelings of loneliness (relational and social connectedness, and self-perceived isolation) of the older person with cancer, measured with the 3-item-UCLA Revised Loneliness Scale.

   [Time Frame: Change from baseline at 24 weeks.]

4. Caregiver burden of close family caregivers
   Caregiver burden of close family caregivers, measured with the Zarit Burden Interview Short Form

   [Time Frame: Change from baseline at 24 weeks.]

Other Pre-specified Outcome Measures:

5. Global health status/quality of life of the older person with cancer
   Global health status/quality of life of the older person with cancer, measured with 2-item subscale from the EORTC-QLQ-C30 (revised) measuring health-related quality of life.

   [Time Frame: Change from baseline at 48 weeks.]

6. Levels of social support of the older person with cancer
   Levels of social support of the older person with cancer measured with the Medical Outcomes Study Social Support Survey (MOS)

   [Time Frame: Change from baseline at 48 weeks.]

7. Feelings of loneliness of the older person with cancer
   Feelings of loneliness (relational and social connectedness, and self-perceived isolation) of the older person with cancer, measured with the 3-item-UCLA Revised Loneliness Scale.

   [Time Frame: Change from baseline at 48 weeks.]

8. Caregiver burden of close family caregivers
   Caregiver burden of close family caregivers, measured with the Zarit Burden Interview Short Form

   [Time Frame: Change from baseline at 48 weeks.]

9. Symptoms or problems experienced
   Symptoms or problems experienced (i.e. as measured by the EORTC-QLQ-C30 symptom subscales and the emotional functioning scale for cancer patients

   [Time Frame: Change from baseline at 24 weeks.]

10. well-being of older people
    well-being of older people (WOOP) (which captures a comprehensive set of well-being domains relevant to older people (broader than health)

[Time Frame: Change from baseline at 24 weeks.]

11. Knowledge of resources and services and confidence in decision making and communicating those decisions
Knowledge of resources and services and confidence in decision making and communicating those decisions (measured with the Nav-CARE engagement questionnaire).

[Time Frame: Change from baseline at 24 weeks.]

12. Health status
Health status EQ-5D (has traditionally been used as outcome measure in economic evaluations)

[Time Frame: Change from baseline at 24 weeks.]

13. Health and social care services and resource use
Health and social care services and resource use (for economic evaluation)

[Time Frame: Change from baseline at 24 weeks.]

14. positive aspects of caregiving of close family caregivers (measured with PAC scale)
positive aspects of caregiving of close family caregivers (measured with PAC scale)

[Time Frame: Change from baseline at 24 weeks.]

Eligibility

Minimum Age:	70 Years
Maximum Age:	
Sex:	All
Gender Based:	No
Accepts Healthy Volunteers:	No
Criteria:	For older person with cancer

Inclusion criteria

- Have a cancer diagnosis (active cancer, meaning not being cancer free, of any stage and involving any treatment/care regimen; i.e. curative, life-extending, or palliative), AND
- Aged 70 years or over, AND
- Have declining or deteriorating health using the Clinical Frailty Scale, AND
- Live at home (own home or home of the family caregiver) (or discharged home if recruited in hospital), AND
- Live within the catchment area of the navigation programme/service

Exclusion criteria

- The close family caregiver living with the person with cancer or providing care at least on a weekly basis, and identified as the primary family caregiver by the person with cancer, if present, does not agree to participate in the study (unless participation is explicitly requested by the patient) , OR
- Lives in a care or nursing home, or is incarcerated, OR
- Currently receives care from a formally recognized community-based multidisciplinary or specialist palliative care team, OR
- Is unable to provide informed consent or has difficulties understanding the information about the study , OR
- Has a psychiatric condition (i.e. schizophrenia, bipolar disorder, or major depressive disorder) OR has an active substance abuse disorder OR
- Is not able to participate in data collection in the country’s language

For close family caregiver (if present)

Inclusion criteria

- Aged 18 years or over , AND
- Lives with the person with cancer OR provides care at least on a weekly basis, AND
- Identified as primary family caregiver by the older person with cancer

Exclusion criteria

- Is unable to provide informed consent or has difficulties understanding the information about the study, OR
- Is not able to participate in data collection in the country's language

Contacts/Locations

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Study Officials: Lieve Van den Block, PhD
Study Principal Investigator
Vrije Universiteit Brussel

Locations:

IPDSharing

Plan to Share IPD: Yes
All IPD that underlie results in a publication will be made available to third parties upon reasonable request and upon signing a unilateral data sharing agreement

Supporting Information:
Study Protocol
Statistical Analysis Plan (SAP)
Analytic Code

Time Frame:
starting 6 months after publication

Access Criteria:
The data can be obtained from the authors of the publication upon reasonable request. Data will be shared with members of universities, scientific research institutions, or clearly separate and independent research departments of public institutions or non- profit organisations. Data may be used for scientific research only (commercial use of data will not be permitted).

URL:

References

Citations:

Links:

Available IPD/Information:	